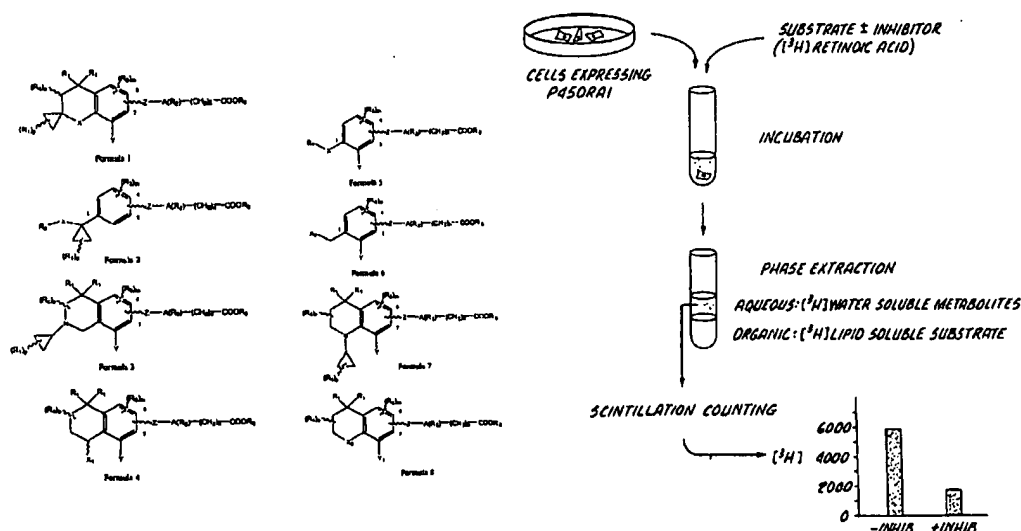


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(54) Title: **METHODS OF PROVIDING AND USING COMPOUNDS HAVING ACTIVITY AS INHIBITORS OF CYTOCHROME P450RA1**

1       METHODS OF PROVIDING AND USING COMPOUNDS HAVING  
2       ACTIVITY AS INHIBITORS OF CYTOCHROME P450RAI  
3       BACKGROUND OF THE INVENTION

4   1. Cross-Reference to Related Application

5       This application is a continuation-in-part of application serial number  
6   09/651,235, filed August 29, 2000.

7   2. Field of the Invention

8       The present invention is directed to providing, preparing and using  
9   compounds which inhibit the enzyme cytochrome P450RAI. More  
10   particularly, the present invention is directed to selecting and preparing  
11   compounds which inhibit the enzyme cytochrome P450RAI, many of which  
12   are derivatives of phenylacetic or heteroarylacetic acid, and using said  
13   compounds for treatment of diseases and conditions which are normally  
14   treated by retinoids.

15                               BACKGROUND ART

16       Compounds which have retinoid-like activity are well known in the art,  
17   and are described in numerous United States and other patents and in scientific  
18   publications. It is generally known and accepted in the art that retinoid-like  
19   activity is useful for treating animals of the mammalian species, including  
20   humans, for curing or alleviating the symptoms and conditions of numerous  
21   diseases and conditions. In other words, it is generally accepted in the art that  
22   pharmaceutical compositions having a retinoid-like compound or compounds  
23   as the active ingredient are useful as regulators of cell proliferation and  
24   differentiation, and particularly as agents for treating skin-related diseases,  
25   including, actinic keratoses, arsenic keratoses, inflammatory and  
26   non-inflammatory acne, psoriasis, ichthyoses and other keratinization and  
27   hyperproliferative disorders of the skin, eczema, atopic dermatitis, Darriers  
28   disease, lichen planus, prevention and reversal of glucocorticoid damage  
29   (steroid atrophy), as a topical anti-microbial, as skin anti-pigmentation agents

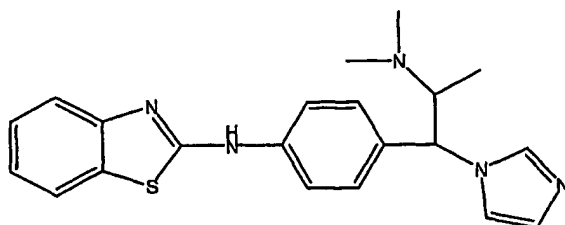
1 and to treat and reverse the effects of age and photo damage to the skin.  
2 Retinoid compounds are also useful for the prevention and treatment of  
3 cancerous and precancerous conditions, including, premalignant and malignant  
4 hyperproliferative diseases such as cancers of the breast, skin, prostate, cervix,  
5 uterus, colon, bladder, esophagus, stomach, lung, larynx, oral cavity, blood  
6 and lymphatic system, metaplasias, dysplasias, neoplasias, leukoplakias and  
7 papillomas of the mucous membranes and in the treatment of Kaposi's  
8 sarcoma. In addition, retinoid compounds can be used as agents to treat  
9 diseases of the eye, including, without limitation, proliferative  
10 vitreoretinopathy (PVR), retinal detachment, dry eye and other corneopathies,  
11 as well as in the treatment and prevention of various cardiovascular diseases,  
12 including, without limitation, diseases associated with lipid metabolism such  
13 as dyslipidemias, prevention of post-angioplasty restenosis and as an agent to  
14 increase the level of circulating tissue plasminogen activator (TPA). Other  
15 uses for retinoid compounds include the prevention and treatment of  
16 conditions and diseases associated with human papilloma virus (HPV),  
17 including warts and genital warts, various inflammatory diseases such as  
18 pulmonary fibrosis, ileitis, colitis and Krohn's disease, neurodegenerative  
19 diseases such as Alzheimer's disease, Parkinson's disease and stroke, improper  
20 pituitary function, including insufficient production of growth hormone,  
21 modulation of apoptosis, including both the induction of apoptosis and  
22 inhibition of T-Cell activated apoptosis, restoration of hair growth, including  
23 combination therapies with the present compounds and other agents such as  
24 Minoxidil<sup>R</sup>, diseases associated with the immune system, including use of the  
25 present compounds as immunosuppressants and immunostimulants,  
26 modulation of organ transplant rejection and facilitation of wound healing,  
27 including modulation of chelosis. Retinoid compounds have relatively  
28 recently been also discovered to be useful for treating type II non-insulin

1 dependent diabetes mellitus (NIDDM).

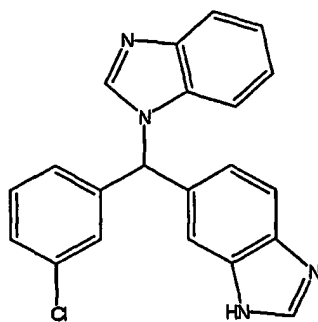
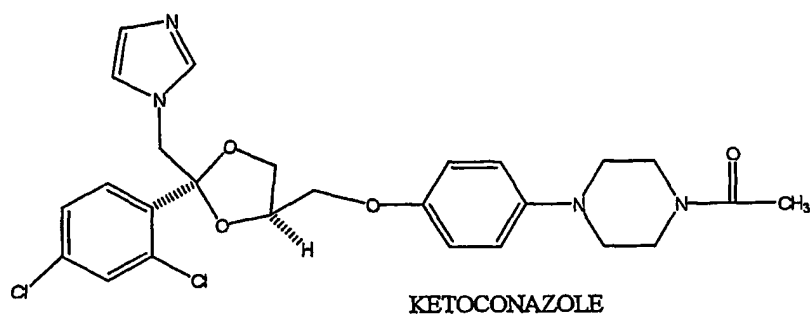
2       Several compounds having retinoid-like activity are actually marketed  
3 under appropriate regulatory approvals in the United States of America and  
4 elsewhere as medicaments for the treatment of several diseases responsive to  
5 treatment with retinoids. Retinoic acid (RA) itself is a natural product,  
6 biosynthesized and present in a multitude of human and mammalian tissues  
7 and is known to play an important rule in the regulation of gene expression,  
8 tissue differentiation and other important biological processes in mammals  
9 including humans. Relatively recently it has been discovered that a catabolic  
10 pathway in mammals, including humans, of natural retinoic acid includes a  
11 step of hydroxylation of RA catalyzed by the enzyme Cytochrome P450RAI  
12 (retinoic acid inducible).

13       Several inhibitors of CP450RAI have been synthesized or discovered in  
14 the prior art, among the most important ones ketoconazole, liarozole and  
15 R116010 are mentioned. The chemical structures of these prior art compounds  
16 are provided below. It has also been noted in the prior art, that administration  
17 to mammals, including humans, of certain inhibitors of CP-450RAI results in  
18 significant increase in endogeneous RA levels, and further that treatment with  
19 CP450RAI inhibitors, for example with liarozole, gives rise to effects similar  
20 to treatment by retinoids, for example amelioration of psoriasis.





R116010



LIARAZOLE

1       The following publications describe or relate to the above-summarized  
2 role of CP450RAI in the natural catabolism of RA, to inhibitors of CP-450RAI  
3 and to *in vitro* and *in vivo* experiments which demonstrate that inhibition of  
4 CP450RAI activity results in a increases endogeneous RA levels and potential  
5 therapeutic benefits:

6 *Kuijpers, et al.*, "The effects of oral liarozole on epidermal proliferation and  
7 differentiation in severe plaque psoriasis are comparable with those of  
8 acitretin", British Journal of Dermatology, (1998) **139**: pp 380-389.

9 *Kang, et al.*, "Liarozole Inhibits Human Epidermal Retinoid Acid 4-  
10 Hydroxylase Activity and Differentially Augments Human Skin Responses to  
11 Retinoic Acid and Retinol *In Vivo*", The Journal of Investigative Dermatology,  
12 (August 1996) **Vol. 107**, No. 2: pp 183-187.

13 *VanWauwe, et al.*, "Liarozole, an Inhibitor of Retinoic Acid Metabolism,  
14 Exerts Retinoid-Mimetic Effects *in Vivo*", The Journal of Pharmacology and  
15 Experimental Therapeutics, (1992) **Vol. 261**, No 2: pp 773-779.

16 *De Porre, et al.*, "Second Generation Retinoic Acid Metabolism Blocking  
17 Agent (Ramba) R116010: Dose Finding in Healthy Male Volunteers",  
18 University of Leuven, Belgium, pp 30.

19 *Wauwe, et al.*, "Ketoconazole Inhibits the *in Vitro* and *in Vivo* Metabolism of  
20 All-*Trans*-Retinoic Acid", The Journal of Pharmacology and Experimental  
21 Therapeutics, (1988) **Vol. 245**, No. 2: pp 718-722.

22 *White, et al.*, "cDNA Cloning of Human Retinoic Acid-metabolizing Enzyme  
23 (hP450RAI) Identifies a Novel Family of Cytochromes P450 (CYP26)\*", The  
24 Journal of Biological Chemistry, (1997) **Vol. 272**, No. 30, Issue of July 25 pp  
25 18538-18541.

26 *Hanzlik, et al.*, "Cyclopropylamines as Suicide Substrates for Cytochromes  
27 P450RAI", Journal of Medicinal Chemistry (1979), **Vol. 22**, No. 7, pp 759-  
28 761.

1 *Ortiz de Montellano*, "Topics in Biology - The Inactivation of Cytochrome  
2 P450RAI", Annual Reports in Medicinal Chemistry, (1984), Chapter 20, pp  
3 201-210.

4 *Hanzlik, et al.* "Suicidal Inactivation of Cytochrome P450RAI by  
5 Cyclopropylamines> Evidence for Cation-Radical Intermediates", J. Am.  
6 Chem. Soc., (1982), Vol. 104, No. 107, pp. 2048-2052.

7 In accordance with the present invention several previously known and  
8 several new compounds are utilized as inhibitors of CP450RAI to provide  
9 therapeutic benefit in the treatment or prevention of the diseases and  
10 conditions which respond to treatment by retinoids and or which in healthy  
11 mammals, including humans, are controlled by natural retinoic acid. The  
12 perceived mode of action of these compounds is that by inhibiting the enzyme  
13 CP450RAI that catabolyzes natural RA, endogenous RA level is elevated to a  
14 level where desired therapeutic benefits are attained. The chemical structures  
15 of certain previously known compounds which have been discovered to be  
16 inhibitors of the enzyme CP450RAI are provided in the descriptive portion of  
17 this application for patent. The chemical structures of the novel compounds  
18 which are used in the methods of treatment in accordance with the invention  
19 are summarized by **Formulas 1 through 8** in the Summary Section of this  
20 application for patent. Based on these chemical structures the following art is  
21 of interest as background to the novel structures.

22 U.S. Patent Nos. 5,965,606; 6,025,388; 5,773,594; 5,675,024;  
23 5,663,347; 5,045,551; 5,023,341; 5,264,578; 5,089,509; 5,616,712; 5,134,159;  
24 5,346,895; 5,346,915; 5,149,705; 5,399,561; 4,980,369; 5,015,658; 5,130,335;  
25 4,740,519; 4,826,984; 5,037,825; 5,466,861; WO 85/00806; EP 0 130,795;  
26 DE 3316932; DE 3708060; *Dawson, et al.* "Chemistry and Biology of  
27 Synthetic Retinoids", published by CRC Press, Inc., (1990), pages 324-356;  
28 are of interest to compounds of **Formula 1**.

1 U.S. Patent Nos. 5,965,606; 5,534,641; 5,663,357; 5,013,744;  
2 5,326,898; 5,202,471; 5,391,753; 5,434,173; 5,498,795; 4,992,468; 4,723,028;  
3 4,855,320; 5,563,292; WO 85/04652; WO 91/16051; WO 92/06948; EP  
4 0 170 105; EP 0 286 364; EP 0 514 269; EP 0 617 020; EP 0 619 116;  
5 DE 3524199; Derwent JP6072866; *Dawson, et al.* "Chemistry and Biology of  
6 Synthetic Retinoids", published by CRC Press, Inc., 1990, pages 324-356; are  
7 of interest to compounds of **Formula 2**.

8 *Dawson, et al.* "Chemistry and Biology of Synthetic Retinoids",  
9 published by CRC Press, Inc., (1990), pages 324-356; is of interest to  
10 compounds of **Formula 3**.

11 U.S. Patent Nos. 5,965,606; 5,773,594; 5,675,024; 5,663,347;  
12 5,023,341; 5,264,578; 5,089,509; 5,149,705; 5,130,335; 4,740,519; 4,826,969;  
13 4,833,240; 5,037, 825; 5,466,861; 5,559,248; WO 85/00806; WO 92/06948;  
14 WO 95/04036; WO 96/05165; EP 0 098 591; EP 0 170 105; EP 0 176 034;  
15 EP 0 253,302; EP 0 303 915; EP 0 514 269; EP 0 617 020; EP 0 619 116;  
16 EP 0 661 259; DE 3316932; DE 3602473; DE 3715955; UK application  
17 GB 2190378; *Eyrolles et al.*, J. Med. Chem., (1994), **37**, 1508-1517; *Graupner*  
18 *et al.* Biochem. and Biophysical Research Communications, (1991), 1554-  
19 1561; *Kagechika, et al.*, J. Med. Chem., (1988), **31**, 2182-2192; *Dawson, et*  
20 *al.* "Chemistry and Biology of Synthetic Retinoids", published by CRC Press,  
21 Inc., (1990), pages 324-356; are of interest to compounds of **Formula 4**.

22 U.S. Patent Nos. 5,965,606; 6,025,388; 5,534,641; 5,663,357;  
23 5,013,744; 5,326,898; 5,202,471; 5,391,753; 5,434,173; 5,498,795; 4,992,468;  
24 5,723,028; 4,855,320; 5,563,292; WO 85/04652; WO 91/16051;  
25 WO 92/06948; EP 0 170 105; EP 0 286 364; EP 0 514 269; EP 0 617 020;  
26 EP 0 619 116; DE 3524199; Derwent JP6072866; *Dawson, et al.* "Chemistry  
27 and Biology of Synthetic Retinoids", published by CRC Press, Inc., (1990),  
28 pages 324-356; are of interest to compounds of **Formula 5**.

1 U.S. Patent Nos. 5,965,606; 6,025,388; 5,534,641; 5,663,357;  
2 5,013,744; 5,326,898; 5,202,471; 5,391,753; 5,434,173; 5,498,795; 4,992,468;  
3 5,723,028; 4,855,320; 5,563,292; WO 85/04652; WO 91/16051;  
4 WO 92/06948; EP 0 170 105; EP 0 286 364; EP 0 514 269; EP 0 617 020;  
5 EP 0 619 116; DE 3524199; Derwert JP6072866; *Dawson, et al.* "Chemistry  
6 and Biology of Synthetic Retinoids", published by CRC Press, Inc., (1990),  
7 pages 324-356; are of interest to compounds of **Formula 6**.

8 U.S. Patent Nos. 6,048,873; 5,663,347; 5,045,551; 5,023,341;  
9 5,739,338; 5,264,578; 5,089,509; 5,616,712; 5,399,561; 4,826,984; 5,037,825;  
10 EP 0 130 795; DE 3316932; *Dawson, et al.* "Chemistry and Biology of  
11 Synthetic Retinoids", published by CRC Press, Inc., (1990), pages 324-356;  
12 are of interest to compounds of **Formula 7**.

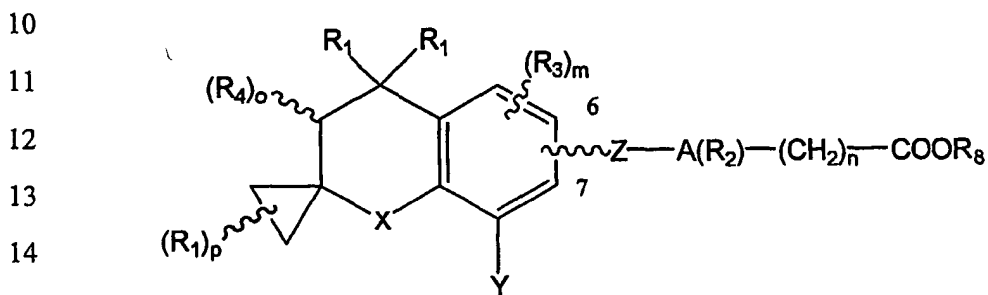
13 U.S. Patent Nos. 5,965,606; 5,998,471; 5,773,594; 5,675,024;  
14 5,663,347; 5,045,551; 5,023,341; 5,264,578; 5,134,159; 5,346,895; 5,346,915;  
15 5,149,705; 5,399,561; 4,980,369; 5,130,335; 4,326,055; 4,539,154; 4,740,519;  
16 4,826,969; 4,826,984; 4,833,240; 5,037,825; 5,466,861; 5,559,248;  
17 WO 85/00806; WO 92/06948; WO 95/04036; WO 96/05165; EP 0 098 591;  
18 EP 0 130 795; EP 0 176 034; EP 0 253 302; EP 0 303 915; EP 0 514 269;  
19 EP 0 617 020; EP 0 619 116; EP 0 661 259; DE 3316932; DE 3602473;  
20 DE 3708060; DE 3715955; U.K. application GB 2190378; *Eyrolles et al.*, J.  
21 Med. Chem., (1994), 37 1508, 1517; *Graupner et al.*, Biochem. and  
22 Biophysical Research Communications, (1991) 1554-1561; *Kagechika, et al.*,  
23 J. Med. Chem., (1988), 31, 2182-2192; *Dawson, et al.* "Chemistry and  
24 Biology of Synthetic Retinoids", published by CRC Press, Inc., (1990), pages  
25 324-356; are of interest to compounds of **Formula 8**.

26 Prior art which is of interest as background to the previously known  
27 compounds that have been discovered in accordance with the present invention  
28 to be inhibitors of cytochrome P450RAI, is identified together with the

1 identification of these known compounds.

## 2 SUMMARY OF THE INVENTION

3 In accordance with the present invention novel compounds of  
 4 **Formulas 1** through **8** are used as inhibitors of the enzyme cytochrome  
 5 P450RAI to treat diseases and conditions which are normally responsible to  
 6 treatment by retinoids, or which are prevented, treated, ameliorated, or the  
 7 onset of which is delayed by administration of retinoid compounds or by the  
 8 mammalian organism's naturally occurring retinoic acid. These novel  
 9 compounds are shown by **Formulas 1**



16 **Formula 1**

17

18 wherein **A** is a phenyl or naphthyl group, or heteroaryl selected from a group  
 19 consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl,  
 20 thiazolyl, oxazolyl, imidazolyl and pyrazolyl, said phenyl and heteroaryl  
 21 groups being optionally substituted with one or two **R<sub>2</sub>** groups;

22 **X** is O, S or NR where **R** is H, alkyl of 1 to 6 carbons or benzyl;

23 **Y** is H, alkyl of 1 to 10 carbons, benzyl, lower alkyl or halogen  
 24 substituted benzyl, fluoro-substituted alkyl of 1 to 10 carbons, cycloalkyl of 3  
 25 to 6 carbons, lower alkyl substituted cycloalkyl of 3 to 6 carbons, Cl, Br, or I;

26 **Z** is -C≡C-,

27 -(CR<sub>1</sub>=CR<sub>1</sub>)<sub>n</sub>, where n' is an integer having the value 1 - 5,

28 -CO-NR<sub>1</sub>-,

1 NR<sub>1</sub>-CO-;

2 -CO-O-,

3 -O-CO-,

4 -CS-NR<sub>1</sub>-,

5 NR<sub>1</sub>-CS-,

6 -CO-S-,

7 -S-CO-,

8 -N=N-;

9 R<sub>1</sub> is independently H or alkyl of 1 to 6 carbons;

10 p is an integer having the values of 0 to 4;

11 R<sub>2</sub> is independently H, alkyl of 1 to 6 carbons, F, Cl, Br, I, CF<sub>3</sub>, fluoro  
12 substituted alkyl of 1 to 6 carbons, alkoxy of 1 to 6 carbons, or alkylthio of 1  
13 to 6 carbons;

14 R<sub>3</sub> is independently alkyl of 1 to 6 carbons, F, Cl, Br, I, fluoro  
15 substituted alkyl of 1 to 6 carbons, OH, SH, alkoxy of 1 to 6 carbons, alkylthio  
16 of 1 to 6 carbons or benzyl;

17 m is an integer having the values 0 to 2;

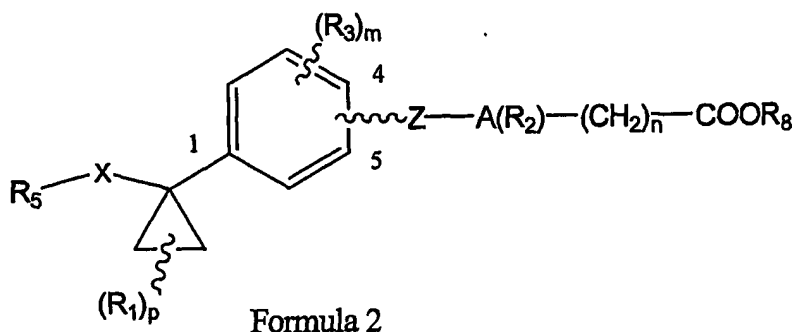
18 R<sub>4</sub> is independently H, alkyl of 1 to 6 carbons, or F; fluorosubstituted  
19 alkyl of 1 to 6 carbons, or halogen;

20 o is an integer having the values of 0 to 2;

21 n is an integer having the values of 0 to 4, and

22 R<sub>8</sub> is H, alkyl of 1 to 6 carbons, -CH<sub>2</sub>O(C<sub>1-6</sub>-alkyl), or a cation of a  
23 pharmaceutically acceptable base.

24 The novel compounds used in the method of treatment of the present  
25 invention are also shown in **Formula 2**



9 wherein A is a phenyl or naphthyl group, or heteroaryl selected from a  
10 group consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl,  
11 thiazolyl, oxazolyl, imidazolyl and pyrazolyl, said phenyl and heteroaryl  
12 groups being optionally substituted with one or two  $R_2$  groups;

13 X is O, S or NR where R is H, alkyl of 1 to 6 carbons or benzyl;

14 Z is  $-C\equiv C-$ ,

15  $-(CR_1=CR_1)_{n'}$ , where  $n'$  is an integer having the value 1 - 5,

16  $-CO-NR_1-$ ,

17  $NR_1-CO-$ ,

18  $-CO-O-$ ,

19  $-O-CO-$ ,

20  $-CS-NR_1-$ ,

21  $NR_1-CS-$ ,

22  $-CO-S-$ ,

23  $-S-CO-$ ,

24  $-N=N-$ ;

25  $R_1$  is independently H or alkyl of 1 to 6 carbons;

26 p is an integer having the values of 0 to 4;

27  $R_2$  is independently H, alkyl of 1 to 6 carbons, F, Cl, Br, I, fluoro

28 substituted alkyl of 1 to 6 carbons, alkoxy of 1 to 6 carbons, or alkylthio of 1



1 to 6 carbons;

2  $R_3$  is independently alkyl of 1 to 6 carbons, F, Cl, Br, I, fluoro  
3 substituted alkyl of 1 to 6 carbons, OH, SH, alkoxy of 1 to 6 carbons, alkylthio  
4 of 1 to 6 carbons or benzyl;

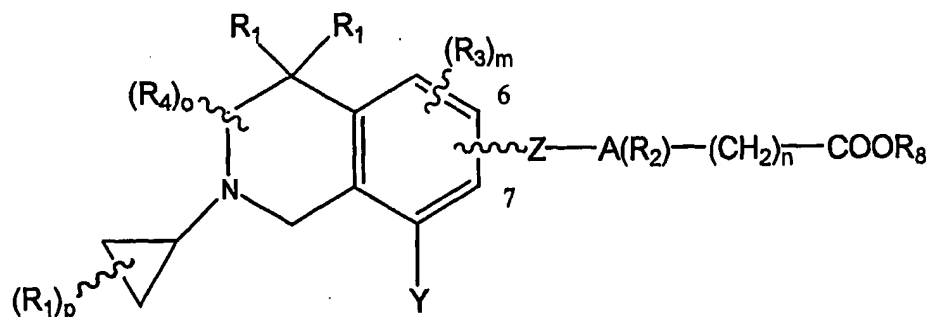
5  $m$  is an integer having the values 0 to 4;

6  $R_5$  is H, alkyl of 1 to 6 carbons, fluorosubstituted alkyl of 1 to 6  
7 carbons, benzyl, or lower alkyl or halogen substituted benzyl;

8  $n$  is an integer having the values of 0 to 4, and

9  $R_8$  is H, alkyl of 1 to 6 carbons,  $-CH_2O(C_{1-6}\text{-alkyl})$ , or a cation of a  
10 pharmaceutically acceptable base.

11 The novel compounds used in the method of treatment of the present  
12 invention are also shown in **Formula 3**

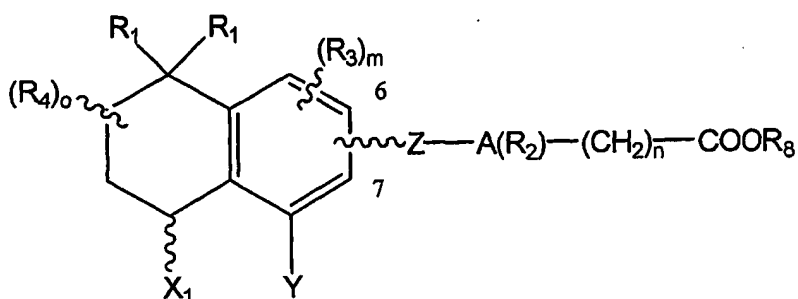


**Formula 3**

22 wherein A is a phenyl or naphthyl group, or heteroaryl selected from a  
23 group consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl,  
24 thiazolyl, oxazolyl, imidazolyl and pyrazolyl, said phenyl and heteroaryl  
25 groups being optionally substituted with one or two  $R_2$  groups;

26 Y is H, alkyl of 1 to 10 carbons, benzyl, lower alkyl or halogen  
27 substituted benzyl, fluoro-substituted alkyl of 1 to 10 carbons, cycloalkyl of 3  
28 to 6 carbons, lower alkyl substituted cycloalkyl of 1 to 6 carbons, Cl, Br, or I;

- 1        **Z** is  $-\text{C}\equiv\text{C}-$ ,  
2         $-(\text{CR}_1=\text{CR}_1)_{n'}$ , where  $n'$  is an integer having the value 1 - 5,  
3         $-\text{CO}-\text{NR}_1-$ ,  
4         $\text{NR}_1-\text{CO}-$ ,  
5         $-\text{CO}-\text{O}-$ ,  
6         $-\text{O}-\text{CO}-$ ,  
7         $-\text{CS}-\text{NR}_1-$ ,  
8         $\text{NR}_1-\text{CS}-$ ,  
9         $-\text{CO}-\text{S}-$ ,  
10        $-\text{S}-\text{CO}-$ ,  
11        $-\text{N}=\text{N}-$ ;  
12       **R<sub>1</sub>** is independently H or alkyl of 1 to 6 carbons;  
13       **p** is an integer having the values of 0 to 5;  
14       **R<sub>2</sub>** is independently H, alkyl of 1 to 6 carbons, F, Cl, Br, I, fluoro  
15 substituted alkyl of 1 to 6 carbons, alkoxy of 1 to 6 carbons, or alkylthio of 1  
16 to 6 carbons;  
17       **R<sub>3</sub>** is independently alkyl of 1 to 6 carbons, F, Cl, Br, I, fluoro  
18 substituted alkyl of 1 to 6 carbons, OH, SH, alkoxy of 1 to 6 carbons, alkylthio  
19 of 1 to 6 carbons or benzyl;  
20       **m** is an integer having the values 0 to 2;  
21       **R<sub>4</sub>** is independently H, alkyl of 1 to 6 carbons, or F; fluorosubstituted  
22 alkyl of 1 to 6 carbons, or halogen;  
23       **o** is an integer having the values of 0 to 4;  
24       **n** is an integer having the values of 0 to 4, and  
25       **R<sub>8</sub>** is H, alkyl of 1 to 6 carbons,  $-\text{CH}_2\text{O}(\text{C}_{1-6}\text{-alkyl})$ , or a cation of a  
26 pharmaceutically acceptable base.  
27       The novel compounds used in the method of treatment of the present  
28 invention are also shown in **Formula 4**



Formula 4

wherein A is a phenyl or naphthyl group, or heteroaryl selected from a group consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl, thiazolyl, oxazolyl, imidazolyl and pyrazolyl, said phenyl and heteroaryl groups being optionally substituted with one or two  $R_2$  groups;

$X_1$  is 1-imidazolyl, or lower alkyl or halogen substituted 1-imidazolyl, OR, SR,  $NRR_6$  where R is H, alkyl of 1 to 6 carbons or benzyl;

Y is H, alkyl of 1 to 10 carbons, benzyl, lower alkyl or halogen substituted benzyl, fluoro-substituted alkyl of 1 to 10 carbons, cycloalkyl of 3 to 6 carbons, lower alkyl substituted cycloalkyl of 3 to 6 carbons, Cl, Br, or I;

Z is  $-C\equiv C-$ ,

$-(CR_1=CR_1)_{n'}$ , where  $n'$  is an integer having the value 1 - 5,

$-CO-NR_1-$ ,

$NR_1-CO-$ ,

$-CO-O-$ ,

$-O-CO-$ ,

$-CS-NR_1-$ ,

$NR_1-CS-$ ,

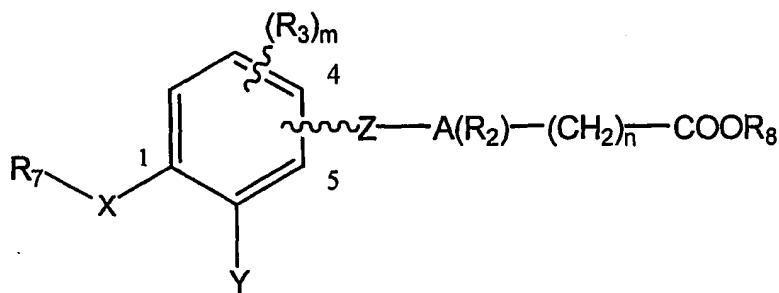
$-CO-S-$ ,

$-S-CO-$ ,

$-N=N-$ ;

$R_1$  is independently H or alkyl of 1 to 6 carbons;

- 1  $R_2$  is independently H, alkyl of 1 to 6 carbons, F, Cl, Br, I, fluoro  
 2 substituted alkyl of 1 to 6 carbons, alkoxy of 1 to 6 carbons, or alkylthio of 1  
 3 to 6 carbons;  
 4  $R_3$  is independently alkyl of 1 to 6 carbons, F, Cl, Br, I, fluoro  
 5 substituted alkyl of 1 to 6 carbons, OH, SH, alkoxy of 1 to 6 carbons, alkylthio  
 6 of 1 to 6 carbons or benzyl;  
 7  $m$  is an integer having the values 0 to 2;  
 8  $R_4$  is independently H, alkyl of 1 to 6 carbons, or F; fluorosubstituted  
 9 alkyl of 1 to 6 carbons, or halogen;  
 10  $o$  is an integer having the values of 0 to 4;  
 11  $R_6$  is H, lower alkyl, cycloalkyl of 3 to 6 carbons, lower alkyl  
 12 substituted cycloalkyl of 3 to 6 carbons;  
 13  $n$  is an integer having the values of 0 to 4, and  
 14  $R_8$  is H, alkyl of 1 to 6 carbons,  $-\text{CH}_2\text{O}(\text{C}_{1-6}\text{-alkyl})$ , or a cation of a  
 15 pharmaceutically acceptable base, with the proviso that when Y is H, A is  
 16 phenyl and  $X_1$  is OH then  $n$  is 1 to 4.  
 17 The novel compounds used in the method of treatment of the present  
 18 invention are also shown in **Formula 5**



Formula 5

1 wherein A is a phenyl or naphthyl group, or heteroaryl selected from a  
2 group consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl,  
3 thiazolyl, oxazolyl, imidazolyl and pyrazolyl, said phenyl and heteroaryl  
4 groups being optionally substituted with one or two  $R_2$  groups;

5 X is O, S or NR where R is H, alkyl of 1 to 6 carbons,  $C_{1-6}$ -trialkylsilyl  
6 or benzyl;

7 Y is H, alkyl of 1 to 10 carbons, benzyl, lower alkyl or halogen  
8 substituted benzyl, fluoro-substituted alkyl of 1 to 10 carbons, cycloalkyl of 3  
9 to 6 carbons, lower alkyl substituted cycloalkyl of 3 to 6 carbons, Cl, Br, or I;

10 Z is  $-C\equiv C-$ ,  
11  $-(CR_1=CR_1)_{n'}$ , where  $n'$  is an integer having the value 1 - 5,  
12  $-CO-NR_1-$ ,  
13  $NR_1-CO-$ ,  
14  $-CO-O-$ ,  
15  $-O-CO-$ ,  
16  $-CS-NR_1-$ ,  
17  $NR_1-CS-$ ,  
18  $-CO-S-$ ,  
19  $-S-CO-$ ,  
20  $-N=N-$ ;

21  $R_1$  is independently H or alkyl of 1 to 6 carbons;

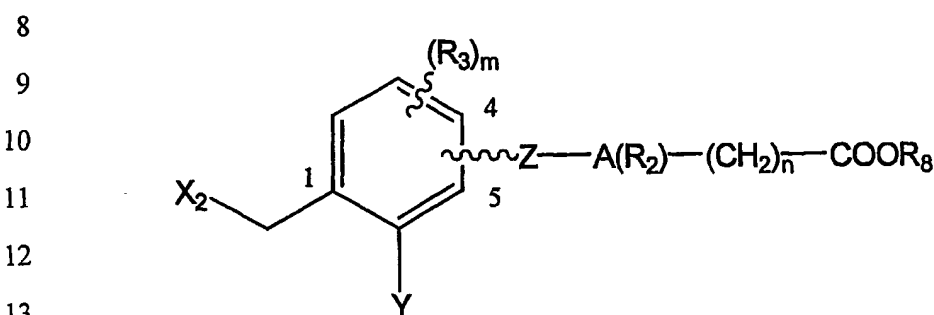
22  $R_2$  is independently H, alkyl of 1 to 6 carbons, F, Cl, Br, I, fluoro  
23 substituted alkyl of 1 to 6 carbons, alkoxy of 1 to 6 carbons, or alkylthio of 1  
24 to 6 carbons;

25  $R_3$  is independently alkyl of 1 to 6 carbons, F, Cl, Br, I, fluoro  
26 substituted alkyl of 1 to 6 carbons, OH, SH, alkoxy of 1 to 6 carbons, alkylthio  
27 of 1 to 6 carbons or benzyl;

28 m is an integer having the values 0 to 3;

1  $R_7$  is H, alkyl of 1 to 6 carbons, cycloalkyl of 3 to 6 carbons or lower  
 2 alkyl substituted cycloalkyl of 1 to 6 carbons;  
 3  $n$  is an integer having the values of 1 to 4, and  
 4  $R_8$  is H, alkyl of 1 to 6 carbons,  $-\text{CH}_2\text{O}(\text{C}_{1-6}\text{-alkyl})$ , or a cation of a  
 5 pharmaceutically acceptable base.

6 The novel compounds used in the method of treatment of the present  
 7 invention are also shown in **Formula 6**



14 **Formula 6**

15 wherein **A** is a phenyl or naphthyl group, or heteroaryl selected from a  
 16 group consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl,  
 17 thiazolyl, oxazolyl, imidazolyl and pyrrazolyl, said phenyl and heteroaryl  
 18 groups being optionally substituted with one or two  $R_2$  groups;

19  $X_2$  is 1-imidazolyl, lower alkyl or halogen substituted 1-imidazolyl,  
 20  $\text{OR}_7$ ,  $\text{SR}_7$  or  $\text{NRR}_7$  where  $R$  is H, alkyl of 1 to 6 carbons or benzyl;

21  $Y$  is H, alkyl of 1 to 10 carbons, benzyl, lower alkyl or halogen  
 22 substituted benzyl, fluoro-substituted alkyl of 1 to 10 carbons, cycloalkyl of 3  
 23 to 6 carbons, lower alkyl substituted cycloalkyl of 3 to 6 carbons, Cl, Br, or I;

24  $Z$  is  $-\text{C}\equiv\text{C}-$ ,  
 25  $-(\text{CR}_1=\text{CR}_1)_{n'}$ , where  $n'$  is an integer having the value 1 - 5,  
 26  $-\text{CO}-\text{NR}_1-$ ,  
 27  $\text{NR}_1-\text{CO}-$ ,  
 28  $-\text{CO}-\text{O}-$ ,

1 -O-CO-,

2 -CS-NR<sub>1</sub>-,

3 NR<sub>1</sub>-CS-,

4 -CO-S-,

5 -S-CO-,

6 -N=N-;

7 R<sub>1</sub> is independently H or alkyl of 1 to 6 carbons;

8 R<sub>2</sub> is independently H, alkyl of 1 to 6 carbons, F, Cl, Br, I, fluoro  
9 substituted alkyl of 1 to 6 carbons, alkoxy of 1 to 6 carbons, or alkylthio of 1  
10 to 6 carbons;

11 R<sub>3</sub> is independently alkyl of 1 to 6 carbons, F, Cl, Br, I, fluoro  
12 substituted alkyl of 1 to 6 carbons, OH, SH, alkoxy of 1 to 6 carbons, alkylthio  
13 of 1 to 6 carbons or benzyl;

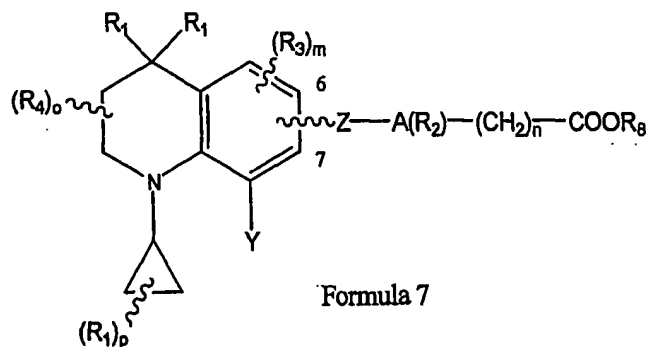
14 m is an integer having the values 0 to 3;

15 R<sub>7</sub> is H, alkyl of 1 to 6 carbons, cycloalkyl of 3 to 6 carbons, lower  
16 alkyl substituted cycloalkyl of 3 to 6 carbons or C<sub>1-6</sub>-trialkylsilyl.

17 n is an integer having the values of 0 to 4, and

18 R<sub>8</sub> is H, alkyl of 1 to 6 carbons, -CH<sub>2</sub>O(C<sub>1-6</sub>-alkyl), or a cation of a  
19 pharmaceutically acceptable base.

20 The novel compounds used in the method of treatment of the present  
21 invention are also shown in Formula 7



1 wherein A is a phenyl or naphthyl group, or heteroaryl selected from a  
2 group consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl,  
3 thiazolyl, oxazolyl, imidazolyl and pyrazolyl, said phenyl and heteroaryl  
4 groups being optionally substituted with one or two  $R_2$  groups;

5 Y is H, alkyl of 1 to 10 carbons, benzyl, lower alkyl or halogen  
6 substituted benzyl, fluoro-substituted alkyl of 1 to 10 carbons, cycloalkyl of 3  
7 to 6 carbons, lower alkyl substituted cycloalkyl of 3 to 6 carbons, F, Cl, Br, or  
8 I;

9 Z is  $-C\equiv C-$ ,  
10  $-(CR_1=CR_1)_n$ , where n' is an integer having the value 1 - 5,  
11  $-CO-NR_1-$ ,  
12  $NR_1-CO-$ ,  
13  $-CO-O-$ ,  
14  $-O-CO-$ ,  
15  $-CS-NR_1-$ ,  
16  $NR_1-CS-$ ,  
17  $-CO-S-$ ,  
18  $-S-CO-$ ,  
19  $-N=N-$ ;

20  $R_1$  is independently H or alkyl of 1 to 6 carbons;

21 p is an integer having the values of 0 to 5;

22  $R_2$  is independently H, alkyl of 1 to 6 carbons, F, Cl, Br, I,  $CF_3$ , fluoro  
23 substituted alkyl of 1 to 6 carbons, alkoxy of 1 to 6 carbons, or alkylthio of 1  
24 to 6 carbons;

25  $R_3$  is independently alkyl of 1 to 6 carbons, F, Cl, Br, I,  $CF_3$ , fluoro  
26 substituted alkyl of 1 to 6 carbons, OH, SH, alkoxy of 1 to 6 carbons, alkylthio  
27 of 1 to 6 carbons or benzyl;

28 m is an integer having the values 0 to 2;



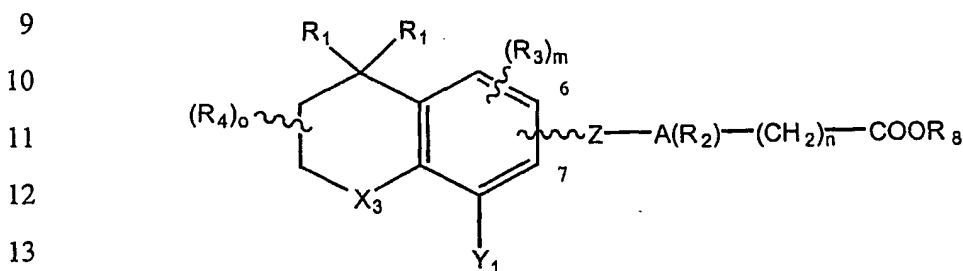
1  $R_4$  is independently H, alkyl of 1 to 6 carbons, or F; fluorosubstituted  
 2 alkyl of 1 to 6 carbons, or halogen;

3  $o$  is an integer having the values of 0 to 4;

4  $n$  is an integer having the values of 0 to 4, and

5  $R_8$  is H, alkyl of 1 to 6 carbons,  $-\text{CH}_2\text{O}(\text{C}_{1-6}\text{-alkyl})$ , or a cation of a  
 6 pharmaceutically acceptable base.

7 The novel compounds used in the method of treatment of the present  
 8 invention are also shown in **Formula 8**



15 **Formula 8**

16 wherein **A** is a phenyl or naphthyl group, or heteroaryl selected from a  
 17 group consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl,  
 18 thiazolyl, oxazolyl, imidazolyl and pyrazolyl, said phenyl and heteroaryl  
 19 groups being optionally substituted with one or two  $R_2$  groups;

20  $X_3$  is S, or O,  $\text{C}(\text{R}_1)_2$ , or CO;

21  $Y_1$  is H, lower alkyl of 1 to 6 carbons, cycloalkyl of 3 to 6 carbons,  
 22 benzyl, lower alkyl substituted cycloalkyl of 3 to 6 carbons;

23  $Z$  is  $-\text{C}\equiv\text{C}-$ ,

24  $-(\text{CR}_1=\text{CR}_1)_n$ , where  $n'$  is an integer having the value 1 - 5,

25  $-\text{CO}-\text{NR}_1-$ ,

26  $\text{NR}_1-\text{CO}-$ ,

27  $-\text{CO}-\text{O}-$ ,

28  $-\text{O}-\text{CO}-$ ,

$-\text{CS}-\text{NR}_1-$ ,

1 NR<sub>1</sub>-CS-,

2 -CO-S-,

3 -S-CO-,

4 -N=N-;

5 R<sub>1</sub> is independently H or alkyl of 1 to 6 carbons;

6 R<sub>2</sub> is independently H, alkyl of 1 to 6 carbons, F, Cl, Br, I, CF<sub>3</sub>, fluoro  
7 substituted alkyl of 1 to 6 carbons, alkoxy of 1 to 6 carbons, or alkylthio of 1  
8 to 6 carbons;

9 R<sub>3</sub> is independently alkyl of 1 to 6 carbons, F, Cl, Br, I, CF<sub>3</sub>, fluoro  
10 substituted alkyl of 1 to 6 carbons, OH, SH, alkoxy of 1 to 6 carbons, alkylthio  
11 of 1 to 6 carbons or benzyl;

12 m is an integer having the values 0 to 2;

13 R<sub>4</sub> is independently H, alkyl of 1 to 6 carbons, or F; fluorosubstituted  
14 alkyl of 1 to 6 carbons, or halogen;

15 o is an integer having the values of 0 to 4;

16 n is an integer having the values of 0 to 4, and

17 R<sub>8</sub> is H, alkyl of 1 to 6 carbons, -CH<sub>2</sub>O(C<sub>1-6</sub>-alkyl), or a cation of a  
18 pharmaceutically acceptable base, the compound meeting at least one of the  
19 provisos selected from the group consisting of:

20 Y<sub>1</sub> is cycloalkyl,

21 when Y<sub>1</sub> is not cycloalkyl then X<sub>3</sub> is O or S and n is 1,

22 when Y<sub>1</sub> is not cycloalkyl then X<sub>3</sub> is CO, and n is 1,

23 when Y<sub>1</sub> is not cycloalkyl then X<sub>3</sub> is CO and the moiety A is  
24 substituted with at least one F group.

25 In accordance with the invention the novel compounds of **Formula 1**  
26 through **Formula 8** as well as the previously known compounds disclosed  
27 below in the specification are used for the prevention or treatment of diseases  
28 and conditions in mammals, including humans, those diseases or conditions

1 that are prevented, treated, ameliorated, or the onset of which is delayed by  
2 administration of retinoid compounds or by the mammalian organism's  
3 naturally occurring retinoic acid. Because the compounds act as inhibitors of  
4 the breakdown of retinoic acid, the invention also relates to the use of the  
5 compounds of **Formula 1** through **Formula 8** in conjunction with retinoic  
6 acid or other retinoids. In this regard it is noted that retinoids are useful for  
7 the treatment of skin-related diseases, including, without limitation, actinic  
8 keratoses, arsenic keratoses, inflammatory and non-inflammatory acne,  
9 psoriasis, ichthyoses and other keratinization and hyperproliferative disorders  
10 of the skin, eczema, atopic dermatitis, Darriers disease, lichen planus,  
11 prevention and reversal of glucocorticoid damage (steroid atrophy), as a  
12 topical anti-microbial, as skin anti-pigmentation agents and to treat and reverse  
13 the effects of age and photo damage to the skin. The retinoids are also useful  
14 for the prevention and treatment of metabolic diseases such as type II non-  
15 insulin dependent diabetes mellitus (NIDDM) and for prevention and  
16 treatment of cancerous and precancerous conditions, including, premalignant  
17 and malignant hyperproliferative diseases such as cancers of the breast, skin,  
18 prostate, cervix, uterus, colon, bladder, esophagus, stomach, lung, larynx, oral  
19 cavity, blood and lymphatic system, metaplasias, dysplasias, neoplasias,  
20 leukoplakias and papillomas of the mucous membranes and in the treatment of  
21 Kaposi's sarcoma. Retinoids can also be used as agents to treat diseases of the  
22 eye, including, without limitation, proliferative vitreoretinopathy (PVR),  
23 retinal detachment, dry eye and other corneopathies, as well as in the treatment  
24 and prevention of various cardiovascular diseases, including, without  
25 limitation, diseases associated with lipid metabolism such as dyslipidemias,  
26 prevention of post-angioplasty restenosis and as an agent to increase the level  
27 of circulating tissue plasminogen activator (TPA). Other uses for retinoids  
28 include the prevention and treatment of conditions and diseases associated

1 with human papilloma virus (HPV), including warts and genital warts, various  
2 inflammatory diseases such as pulmonary fibrosis, ileitis, colitis and Krohn's  
3 disease, neurodegenerative diseases such as Alzheimer's disease, Parkinson's  
4 disease and stroke, improper pituitary function, including insufficient  
5 production of growth hormone, modulation of apoptosis, including both the  
6 induction of apoptosis and inhibition of T-Cell activated apoptosis, restoration  
7 of hair growth, including combination therapies with the present compounds  
8 and other agents such as Minoxidil<sup>R</sup>, diseases associated with the immune  
9 system, including use of the present compounds as immunosuppressants and  
10 immunostimulants, modulation of organ transplant rejection and facilitation of  
11 wound healing, including modulation of chelosis.

12 This invention also relates to a pharmaceutical formulation comprising  
13 one or more compounds of **Formula 1** through **Formula 8** or one or more of  
14 the previously known compounds disclosed below in the specification, in  
15 admixture with a pharmaceutically acceptable excipient, said formulation  
16 being adapted for administration to a mammal, including a human being, to  
17 treat or alleviate the conditions which were described above as treatable by  
18 retinoids, or which are controlled by or responsive to the organism's native  
19 retinoic acid. These formulations can also be co-administered with retinoids to  
20 enhance or prolong the effects of medications containing retinoids or of the  
21 organism's native retinoic acid.

22 The present invention also relates to a method of providing a compound  
23 which is an inhibitor of the enzyme cytochrome P450RAI, wherein the method  
24 of providing the cytochrome P450RAI inhibitory compound comprises:

25 identifying a compound that has activity as a retinoid in any of the art  
26 recognized assays which demonstrate retinoid-like activity, the retinoid  
27 compound having a formula such that it includes a benzoic acid, benzoic acid  
28 ester, naphthoic acid, naphthoic acid ester or heteroaryl carboxylic acid or

1 ester moiety, with a partial structure of  $-A(R_2)-(CH_2)_n-COOR_8$  where the  
2 symbols are defined as in **Formulas 1** through **8**, and where **n** is 0, and  
3 selecting a compound that is a homolog of the previously identified  
4 retinoid compound where in the formula of the homolog **n** is 1 or 2, preferably  
5 1. Said homolog, if it is not a previously known compound can be prepared  
6 by homologation procedures well known to the synthetic organic chemist,  
7 such as for example the well known *Arndt-Eistert* synthesis. Alternatively,  
8 said homologs can be prepared by any of the applicable synthetic processes  
9 illustrated below for the preparation of the novel compounds of **Formulas 1**  
10 through **8** wherein the symbol **n** represents the integral 1 (one).

#### 11 BRIEF DESCRIPTION OF THE DRAWING FIGURE

12 Figure 1 is a schematic representation of the P450RAI cell based assay  
13 utilized to evaluate the ability of the compounds of the invention to inhibit the  
14 Cytochrome P450RAI enzyme.

#### 15 BIOLOGICAL ACTIVITY, MODES OF ADMINISTRATION

##### 16 P450RAI-1 Cell-Based Inhibitor Assay:

17 **Figure 1** shows a schematic diagram of the P450RAI-1 cell based  
18 assay. P450RAI-1 stably transfected HeLa cells are maintained in 100  
19 millimolar tissue culture dishes in Modified Eagle's Medium (MEM)  
20 containing 10 % Fetal Bovine Serum (FBS) and 100 µg/ml hygromycin.  
21 Exponentially growing cells are harvested by incubating in trypsin. Cells are  
22 then washed with 1X Phosphate Buffered Saline (PBS) and plated in a 48-well  
23 plate at  $5 \times 10^5$  cells in 0.2 ml MEM medium containing 10 % FBS and 0.05  
24 µCi [ $^3H$ ]-RA in the presence or absence of increasing concentrations of the test  
25 compounds. The compounds are diluted in 100% DMSO and then added in  
26 triplicate wells at either 10, 1 or 0.1 µM final concentration. As a positive  
27 control for RA metabolism inhibition, cells are also incubated with  
28 ketoconazole at 100, 10 and 1 µM. Cell are incubated for 3 hours at 37°C.

1 The retinoids are then extracted using the procedure of *Bligh et al.* (1959)  
2 Canadian Journal of Biochemistry 37, 911-917, modified by using  
3 methylenechloride instead of chloroform. The publication *Bligh et al.* (1959)  
4 Canadian Journal of Biochemistry 37, 911-917 is specifically incorporated  
5 herein by reference. The water soluble radioactivity is quantified using a  $\beta$ -  
6 scintillation counter.  $IC_{50}$  values represent the concentration of inhibitor  
7 required to inhibit all-*trans*-RA metabolism by 50 percent and are derived  
8 manually from log-transformed data. The  $IC_{50}$  values obtained in this assay  
9 for several novel compounds used in accordance with the invention are  
10 disclosed in **Table 1** below. The  $IC_{50}$  values obtained in this assay for  
11 several previously known compounds the cytochrome P450RAI inhibitory  
12 activity of which has been discovered in accordance with the present  
13 invention, are disclosed in **Table 1A** below.

14 Assays of Retinoid-like or Retinoid Antagonist and Inverse Agonist-like  
15 Biological Activity

16 Assays described below measure the ability of a compound to bind to,  
17 and/or activate various retinoid receptor subtypes. When in these assays a  
18 compound binds to a given receptor subtype and activates the transcription of  
19 a reporter gene through that subtype, then the compound is considered an  
20 **agonist** of that receptor subtype. Conversely, a compound is considered an  
21 **antagonist** of a given receptor subtype if in the below described co-transfection  
22 assays the compound does not cause significant transcriptional activation of  
23 the receptor regulated reporter gene, but nevertheless binds to the receptor  
24 with a  $K_d$  value of less than approximately 1 micromolar. In the below  
25 described assays the ability of the compounds to bind to  $RAR_\alpha$ ,  $RAR_\beta$ ,  $RAR_\gamma$ ,  
26  $RXR_\alpha$ ,  $RXR_\beta$  and  $RXR_\gamma$  receptors, and the ability or inability of the  
27 compounds to activate transcription of a reporter gene through these receptor  
28 subtypes can be tested.

1 As far as specific assays are concerned, a **chimeric receptor**  
2 **transactivation assay** which tests for agonist-like activity in the RAR $\alpha$ , RAR $\beta$ ,  
3 and RAR $\gamma$ , receptor subtypes, and which is based on work published by  
4 *Feigner P. L. and Holm M.* (1989) Focus, 112 is described in detail in United  
5 States Patent No. 5,455,265. The specification of United States Patent No.  
6 5,455,265 is hereby expressly incorporated by reference. The numeric results  
7 obtained with several preferred novel compounds used in accordance with the  
8 invention in this assay are shown below in **Table 1**. These data demonstrate  
9 that generally speaking the compounds of **Formulas 1** through **8**, are not  
10 agonists (or only weak agonists) of RAR retinoic receptors, and also that they  
11 do not bind, or in some cases bind only weakly to RAR retinoid receptors.

12 A **holoreceptor transactivation assay** and a **ligand binding assay**  
13 which measure the antagonist/agonist like activity of the compounds used in  
14 accordance with the invention, or their ability to bind to the several retinoid  
15 receptor subtypes, respectively, are described in published PCT Application  
16 No. WO WO93/11755 (particularly on pages 30 - 33 and 37 - 41) published on  
17 June 24, 1993, the specification of which is also incorporated herein by  
18 reference. A detailed experimental procedure for holoreceptor  
19 transactivations has been described by *Heyman et al.* Cell 68, 397 - 406,  
20 (1992); *Allegretto et al.* J. Biol. Chem. 268, 26625 - 26633, and *Mangelsdorf*  
21 *et al.* The Retinoids: Biology, Chemistry and Medicine, pp 319 - 349, Raven  
22 Press Ltd., New York, which are expressly incorporated herein by reference.  
23 The results obtained in this assay are expressed in EC<sub>50</sub> numbers, as they are  
24 also in the **chimeric receptor transactivation assay**. The results of **ligand**  
25 **binding assay** are expressed in K<sub>d</sub> numbers. (See *Cheng et al.* Biochemical  
26 Pharmacology Vol. 22 pp 3099-3108, expressly incorporated herein by  
27 reference.)

28 The results if the ligand binding assay for several preferred novel

1 compounds used in accordance with the invention are included in Table 1. In  
 2 the holoreceptor transactivation assay, tested for RXR $_{\alpha}$ , RXR $_{\beta}$ , and RXR $_{\gamma}$   
 3 receptors, the novel compounds are, generally speaking, entirely devoid of  
 4 activity, demonstrating that the novel compounds do not act as RXR agonists.

TABLE 1

Compound #	General Formula	Table # <sup>1</sup>	RAR EC <sub>50</sub> /(EFFICACY)/K <sub>d</sub> nM			P450RAI INHIBITION DATA
			$\alpha$	$\beta$	$\gamma$	INTACT HELA IC <sub>50</sub> $\mu$ M
110	2	3	NA 2058	74 (44) 409	262 (42) >10K	>10
112	2	3	NA 5853	335 (37) 704	NA 685	>10
3	4	5	280 (28) 145	4.8 (54) 0.8	9.8 (52) 158	3
114	2	3	NA >10K	NA >10K	NA >10K	>10
108	2	3	6.6 (15) 21K	283 (36) 547	141 (10) 13K	>10
116	2	3	NA 3269	WA 732	NA 886	>10
77	2	3	NA 2207	WA 225	NA 16	>10
78	2	3	NA >10K	NA >10K	NA >10K	>10



1	40	1	2	33 (207) 69	1.2 (126) 1.3	6.8 (140) 363	1.7
2	42	1	2	NA 15K	NA 3636	NA >10K	0.19
3	28	8	9	NA 21K	NA 4272	NA >10K	0.34
4	70	2	3	NA >10K	NA >10K	NA >10K	>10
5	69	2	3	313 (10) 469	12 (50) 133	52.6 (31) 501	>10
6	73	2	3	WA 486	22.5 (39) 26	91 (24) 351	>10
7	74	2	3	NA 11K	NA 14K	NA >10K	3.5
8	30	8	9	14	2.2	84	0.28
9	44	1	2	49 (138) 37	1.7 (100) 1.9	7.5 (116) 392	0.27
10	82	2	3	NA >10K	NA >10K	NA >10K	>10
11	81	2	3	NA 4210	490 (80) 846	183 (67) 1058	>10
12	89	2	3	268 (20) 3407	26 (50) 980	12 (46) 475	>10

1	90	2	3	NA >10K	NA >10K	NA >10K	0.95
2	94	2	3	NA >10K	NA >10K	NA >10K	>10
3	93	2	3	4821 (114) 3450	20 (39) 554	10 (55) 358	>10
4	5	8	9	NA 9148	11 (36) 2815	NA >10K	0.55
5	8	4	5	NA 10K	363 (96) 3781	NA 25K	0.4
6	86	2	3	NA >10K	NA >10K	NA >10K	1.4
7	85	2	3	976 (60) 1861	3.5 (77) 240	2.5 (65) 302	>10
8	98	2	3	NA	NA	NA	0.8
9	13	4	5	NA	3.2 (6.6)	116 (9)	3.1
10	10	8	9	57 (146)	0.3 (86)	6 (94)	0.7
11	36	8	9	13K	4896	492	0.033
12	38	8	9	10K	5317	2884	0.025

1	34	8	9	61.5	15	2.5	0.13
2	119	6	7	>10K	>10K	>10K	0.4
3	121	6	7	>10K	>100K	>100K	0.18
4	46	8	9	>10K	>10K	>10K	2.2
5	20	8	9				>10
6	18	4	5				1.1
7	32	8	9	27K	4225	13K	0.18
8	139	4	5				0.05
9	22	3	4				1.6
10	24	3	4				3
11	137	4	5				0.1
12	26	4	5				10
13	127	6	7				0.4
14	126	6	7				0.09
15	48	1	2				0.03

1	50	1	2				0.014
2	52	1	2				0.05
3	54	1	2				0.022
4	62	7	8				>10
5	56	8	9				0.13
6	134	6	7				5
7	58	1	2				0.18
8	60	1	2				1.6
9	143						0.8
10	145						0.2

11  
12 <sup>1</sup>The "Table #" refers to Table 2 through 9 provided below where the  
13 compound is identified with reference to a corresponding specific formula of  
14 **Formulas 9 through 16.**

15  
16 **Table 1A** below provides data similar to those provided in **Table 1**, for  
17 certain previously known compounds which have been discovered in  
18 accordance with the present invention to be useful as inhibitors of cytochrome  
19 P450RAI. These compounds are shown by **Formula A** through **O** and have  
20 **compounds numbers 201 through 247.**

21

TABLE 1A

Compound #	General Formula	RAR EC <sub>50</sub> /(EFFICACY)/K <sub>d</sub> nM			P450RAI INHIBITION DATA
		$\alpha$	$\beta$	$\gamma$	INTACT HELA IC <sub>50</sub> $\mu$ M
201	A	>10K 300 90	>10K (12) 1105	180 (24) 4391	0.52
202	A				0.6
203	C				0.62
204	C				0.7
205	C				1
206	C				1.8
207	D				1.2
208	D				1
209	E				1.7
210	A	89 (25) 10000	18 (122) 2891	15 (61) 10000	10
211	E				1.5
212	G				7
214	E				1.9
215	A				6.2
216	D				3.3
217	G				6.3
218	D				3.4
219	G				3.2
220	C				1
221	C				>10
222	F				>10

1	223	F				>10
2	224	C				5.5
3	225	C				>10
4	226	C				>10
5	227	C				1.3
6	228	C				6
7	229	G				1.6
8	230	D				5.1
9	231	K				4.1
10	232	D				4.2
11	233	M				1.3
12	234	M				4.7
13	235	E				7
14	236	E				5.5
15	237	J				6.8
16	238	A				7.2
17	240	B				3
18	241	N				5.5
19	242	I				5.8
20	243	L				7.4
21	244	G				5.1
22	245	H				3.3
23	246	J				3.1
24	247	O				10
25						

## TOPICAL SKIN IRRITATION TESTS

1  
2 As is known the topical retinoid all-trans-retinoic acid (ATRA) and oral  
3 retinoids such as 13-cis RA and etretinate are known to induce substantial skin  
4 irritation in humans. This irritation is a direct result of activation of the RAR  
5 nuclear receptors. Analysis of retinoid topical irritation is also a highly  
6 reproducible method of determining *in vivo* retinoid potency. The SKH1-  
7 *hrBR* or hairless mouse provides a convenient animal model of topical  
8 irritation, since retinoid-induced skin flaking and abrasion can be readily  
9 scored by eye (*Standeven et al.*, "Specific antagonist of retinoid toxicity in  
10 mice." Toxicol. Appl. Pharmacol., 138:169-175, (1996); *Thacher, et al.*,  
11 "Receptor specificity of retinoid-induced hyperplasia. Effect of RXR-selective  
12 agonists and correlation with topical irritation". J. Pharm. Exp. Ther., 282:528-  
13 534, (1997)). As is demonstrated below the topical application of P450RAI  
14 inhibitors in accordance with the present invention also causes an increase in  
15 the endogenous levels of ATRA that results in ATRA-induced irritation in  
16 skin of hairless mice. The attached data table discloses the retinoid-mimetic  
17 effects of some P450RAI inhibitor compounds in accordance with the present  
18 invention on the skin of hairless mice.

## Methods

20 Female hairless mice (CrI:SKH1-*hrBR*), 5-7 weeks old, were obtained  
21 from Charles River Breeding Labs (Wilmington, MA). Animals were about 6  
22 weeks old at the start of the experiments. Food (Purina Rodent Chow 5001)  
23 and reverse osmosis water were provided *ad libitum*. Mice were housed  
24 individually throughout the dosing period. In some experiments, mice that fit  
25 within a defined weight range, e.g., 21-25g, were selected from the available  
26 stock and then randomly assigned to the various treatment groups, using body  
27 weight as the randomization variable.

28 The compounds to be tested were dissolved in acetone for application

1 to the backs of the mice.

2 Mice were treated topically on the back in a volume of 4.0 ml/kg (0.07-  
3 0.12ml) adjusted daily so as to deliver a fixed dose of test compound per g  
4 body weight. Doses are disclosed as nmol/25g.

5 Unless indicated otherwise, mice were treated with retinoids once daily  
6 on days 1 through 5 and observed on days 2, 3, 4, 5, 6, 7 and 8.

7 The mice were weighed daily and the dorsal skin was graded daily  
8 using separate semi-quantitative scales to determine flaking and abrasion.  
9 These flaking and abrasion scores were combined with weight change (if any)  
10 to create a cutaneous toxicity score (Blackjack score).

#### 11 Cutaneous Toxicity Score

12 A visual grading scale was used for characterizing topical irritation on a  
13 daily basis. The grading scale used is as follows:

14

15	<u>Flaking</u>	<u>Abrasions</u>
16	0 = none	0 = none
17	1 = slight (small flakes, <50%	1 = slight (one or two abrasions with
18	coverage)	a light pink color)
19	2 = mild (small flakes, 50%	2 = mild (several abrasions with a
20	coverage)	pink color)
21	3 = moderate (small flakes, >50%	3 = moderate (one or two deep
22	coverage & large flakes, <25%	abrasions with red color, <25%
23	coverage)	coverage)
24	4 = severe (small flakes, >50%	4 = severe (multiple deep abrasions
25	coverage & large flakes, 25-50%	with red color, >25% coverage)
26	coverage)	
27	5 = very severe (large flakes, >50%	
28	coverage)	
29		



1    Topical Toxicity Score

2            The flaking and abrasion observations were combined with body  
3 weight observations to calculate a single, semiquantitative topical or cutaneous  
4 "toxicity score" as detailed below. The toxicity score (also known as  
5 "blackjack score" since the theoretical maximum is 21) takes into account the  
6 maximal severity, and the time of onset of skin flaking and abrasions and the  
7 extent of weight between the first and last days of the experiment. Below are  
8 listed the seven numerical components of the toxicity score and an explanation  
9 of how those values are combined to calculate the toxicity score.

10           1.    Flaking-Maximal Severity:

11                   Highest flaking score attained during observation period.

12           2.    Flaking-Day of Onset of grade 2 or worse:

13                   0 - > 8 days

14                   1 - day 8

15                   2 - day 6 or 7

16                   3 - day 4 or 5

17                   4 - day 2 or 3

18           3.    Flaking-Average Severity:

19                   Flaking severity scores are summed and divided by the number  
20                   of observation days.

21           4.    Abrasion-Maximal Severity:

22                   Highest abrasion score attained during observation period.

23           5.    Abrasion-Day of Onset of grade 2 or worse:

24                   Same scale as (2) above.

25           6.    Abrasion-Average Severity:

26                   Abrasion severity scores are summed and divided by the number  
27                   of observation days.

28           7.    Systemic Toxicity (weight loss):

- 1                   0 - <1g
- 2                   1 - 1 to 2g
- 3                   2 - 2 to 4g
- 4                   3 - 4 to 6g
- 5                   4 - >6g or dead

6   Calculation of Composite Flaking Score

7           Flaking onset score (2) and average severity score (3) are summed and  
8   divided by two. The quotient is added to the maximal severity score (1).  
9   Composite flaking scores are calculated for each individual animal in a group,  
10   averaged, and rounded to the nearest integer. Values can range from 0-9.

11   Calculation of Composite Abrasion Score

12           Abrasion onset score (5) and average severity score (6) are summed and  
13   divided by two. The quotient is added to the maximal severity score (4).  
14   Composite abrasion scores are calculated for each individual animal in a  
15   group, averaged and rounded to the nearest integer. Values can range from 0-  
16   8.

17   Calculation of Toxicity Score

18           Composite flaking score, composite abrasion score, and systemic  
19   toxicity score are summed to give the "toxicity score." Toxicity scores are  
20   calculated for each individual animal in a group, averaged, and rounded to the  
21   nearest integer. Values can range from 0-21 and are expressed in **Table 1B**  
22   below as the mean  $\pm$  SD of the values for a group.

23   Calculation of Percentage Change in Body Weight

24           The body weight at the time of the last weighing (day 8, 11, or 12) was  
25   subtracted from the initial body weight. The difference was divided by the  
26   initial body weight, multiplied by 100%, and rounded to the nearest integer.  
27   Values were calculated for each individual animal and the mean and standard  
28   deviation for each group are shown.

TABLE 1B

Compound No.	Cutaneous Toxicity Score (Blackjack Score)		
	100 nmole	300 nmole	1000 nmole
5	0		6±3
15	1 ± 1		5 ± 2
36	1 ± 1		11 ± 0
38	1 ± 1		10 ± 1
8	5 ± 2	8 ± 3	12 ± 1
22	0 ± 0	0 ± 0	1 ± 1
137	1 ± 1	1 ± 1	5 ± 2
48	1 ± 1	3 ± 1	7 ± 2
50	1 ± 0	3 ± 2	8 ± 2
58	0 ± 0	0 ± 0	0 ± 0
131	1 ± 1	0 ± 1	1 ± 1
127	0 ± 0	0 ± 0	0 ± 0
18	0 ± 0	5 ± 2	10 ± 2
247	1 ± 0	2 ± 1	6 ± 1

Modes of Administration

The compounds used in the methods of treatment of this invention may be administered systemically or topically, depending on such considerations as the condition to be treated, need for site-specific treatment, quantity of drug to be administered, and numerous other considerations. Thus, in the treatment of dermatoses, it will generally be preferred to administer the drug topically, though in certain cases such as treatment of severe cystic acne or psoriasis, oral administration may also be used. Any common topical formulation such

1 as a solution, suspension, gel, ointment, or salve and the like may be used.  
2 Preparation of such topical formulations are well described in the art of  
3 pharmaceutical formulations as exemplified, for example, by Remington's  
4 Pharmaceutical Science, Edition 17, Mack Publishing Company, Easton,  
5 Pennsylvania. For topical application, the compounds could also be  
6 administered as a powder or spray, particularly in aerosol form. If the drug is  
7 to be administered systemically, it may be confectioned as a powder, pill, tablet or  
8 the like or as a syrup or elixir suitable for oral administration. For intravenous  
9 or intraperitoneal administration, the compound will be prepared as a solution  
10 or suspension capable of being administered by injection. In certain cases, it  
11 may be useful to formulate these compounds by injection. In certain cases, it  
12 may be useful to formulate these compounds in suppository form or as  
13 extended release formulation for deposit under the skin or intramuscular  
14 injection.

15 Other medicaments can be added to such topical formulation for such  
16 secondary purposes as treating skin dryness; providing protection against light;  
17 other medications for treating dermatoses; medicaments for preventing  
18 infection, reducing irritation, inflammation and the like.

19 Treatment of dermatoses or any other indications known or discovered  
20 to be susceptible to treatment by retinoic acid-like compounds, or to control by  
21 naturally occurring retinoic acid will be effected by administration of the  
22 therapeutically effective dose of one or more compounds used in accordance  
23 with the instant invention. A therapeutic concentration will be that  
24 concentration which effects reduction of the particular condition, or retards its  
25 expansion. In certain instances, the compound potentially may be used in  
26 prophylactic manner to prevent onset of a particular condition.

27 A useful therapeutic or prophylactic concentration will vary from  
28 condition to condition and in certain instances may vary with the severity of

1 the condition being treated and the patient's susceptibility to treatment.  
2 Accordingly, no single concentration will be uniformly useful, but will require  
3 modification depending on the particularities of the disease being treated.  
4 Such concentrations can be arrived at through routine experimentation.  
5 However, it is anticipated that in the treatment of, for example, acne, or similar  
6 dermatoses, that a formulation containing between 0.01 and 1.0 milligrams per  
7 milliliter of formulation will constitute a therapeutically effective  
8 concentration for total application. If administered systemically, an amount  
9 between 0.01 and 5 mg per kg of body weight per day would be expected to  
10 effect a therapeutic result in the treatment of many diseases for which these  
11 compounds are useful.

12 In some applications pharmaceutical formulations containing the CP-  
13 450RAI inhibitory compounds may be co-administered with formulations  
14 containing retinoids. In such cases the dose of the cytochrome P450RAI  
15 inhibitors compounds is in the range of 0.01 and 5 mg per kg body weight per  
16 day.

## 17 GENERAL EMBODIMENTS AND SYNTHETIC METHODOLOGY

### 18 Definitions

19 The term alkyl refers to and covers any and all groups which are known  
20 as normal alkyl and branched-chain alkyl. Unless specified otherwise, lower  
21 alkyl means the above-defined broad definition of alkyl groups having 1 to 6  
22 carbons in case of normal lower alkyl, and 3 to 6 carbons for lower branch  
23 chained alkyl groups. A pharmaceutically acceptable salt may be prepared for  
24 any compound used in accordance with the invention having a functionality  
25 capable of forming a salt, for example an acid functionality. A  
26 pharmaceutically acceptable salt is any salt which retains the activity of the  
27 parent compound and does not impart any deleterious or untoward effect on  
28 the subject to which it is administered and in the context in which it is

1 administered.

2       Pharmaceutically acceptable salts may be derived from organic or  
3 inorganic bases. The salt may be a mono or polyvalent ion. Of particular  
4 interest are the inorganic ions, sodium, potassium, calcium, and magnesium.  
5 Organic salts may be made with amines, particularly ammonium salts such as  
6 mono-, di- and trialkyl amines or ethanol amines. Salts may also be formed  
7 with caffeine, tromethamine and similar molecules. Where there is a nitrogen  
8 sufficiently basic as to be capable of forming acid addition salts, such may be  
9 formed with any inorganic or organic acids or alkylating agent such as methyl  
10 iodide. Preferred salts are those formed with inorganic acids such as  
11 hydrochloric acid, sulfuric acid or phosphoric acid. Any of a number of  
12 simple organic acids such as mono-, di- or tri- acid may also be used.

13       Some compounds used in accordance with the present invention may  
14 have *trans* and *cis* (E and Z) isomers. Unless specific orientation of  
15 substituents relative to a double bond or a ring is indicated in the name of the  
16 respective compound, and/or by specifically showing in the structural formula  
17 the orientation of the substituents relative to the double bond or ring the  
18 invention covers *trans* as well as *cis* isomers.

19       Some of the compounds used in accordance with the present invention  
20 may contain one or more chiral centers and therefore may exist in  
21 enantiomeric and diastereomeric forms. The scope of the present invention is  
22 intended to cover all isomers *per se*, as well as mixtures of *cis* and *trans*  
23 isomers, mixtures of diastereomers and racemic mixtures of enantiomers  
24 (optical isomers) as well. A bond drawn with a wavy line indicates that the  
25 carbon to which the bond is attached can be in any of the applicable possible  
26 configurations.

## 27 General Synthetic Methodology

28       The novel compounds used in accordance with the invention are

1 encompassed by the general **Formulas 1** through **8** provided above. The  
2 previously known compounds the cytochrome P450RAI activity of which has  
3 been discovered in accordance with the present invention are identified below,  
4 and references are provided which enable their preparation by one of  
5 ordinary skill in the art of synthetic organic chemistry. In each of these  
6 formulas a linker or tethering group designated **Z** covalently connects an  
7 aromatic or heteroaromatic moiety designated  $A(R_2)-(CH_2)_n-COOR_8$  and  
8 another cyclic moiety which in accordance with these formulas is a substituted  
9 phenyl, substituted tetrahydronaphthalene, substituted chroman, thiochroman,  
10 tetrahydroquinoline or tetrahydroisoquinoline moiety. Generally speaking a  
11 compound such as  $X_4-A(R_2)-(CH_2)_n-COOR_8$  is commercially available, or  
12 can be made in accordance with the chemical literature, or with such  
13 modification of known chemical processes which are within the skill of the  
14 practicing organic chemist. The group  $X_4$  represents a reactive group, which  
15 is suitable for coupling the  $X_4-A(R_2)-(CH_2)_n-COOR_8$  compound to a  
16 derivative of the substituted phenyl, substituted tetrahydronaphthalene,  
17 substituted chroman, thiochroman, tetrahydroquinoline or  
18 tetrahydroisoquinoline moiety so that as a result of the coupling the linker or  
19 tether moiety **Z** is formed. In many instances the group  $X_4$  is a leaving group  
20 such as halogen, or trifluoromethanesulfonyloxy, or a group capable of  
21 participating in a *Wittig* or *Horner Emmons* reaction. In some instances the  
22 group  $X_4$  is an ethynyl group capable of undergoing a coupling reaction with a  
23 leaving group (such as a halogen or a trifluoromethanesulfonyloxy group)  
24 attached to the substituted phenyl, substituted tetrahydronaphthalene,  
25 substituted chroman, thiochroman, tetrahydroquinoline or  
26 tetrahydroisoquinoline moiety. The group  $X_4$  can also represent an OH or an  
27  $NH_2$  group that forms an ester (COO) or amide (CONH) linker, respectively,  
28 when reacted with an activated carboxyl derivative of the substituted phenyl,

1 substituted tetrahydronaphthalene, substituted chroman, thiochroman,  
2 tetrahydroquinoline or tetrahydroisoquinoline moiety. Examples for the  
3 compounds of formula  $X_4-A(R_2)-(CH_2)_n-COOR_8$  are provided in the specific  
4 examples below. Further examples where the  $X_4$  group is halogen are ethyl  
5 4-iodobenzoate, ethyl 6-iodonicotinate, ethyl 5-iodofuran-3-carboxylate, ethyl  
6 5-iodothiophen-3-carboxylate, ethyl 5-iodofuran-2-carboxylate, ethyl 5-  
7 iodothiophen-2-carboxylate, and analogous halogenated derivatives of the  
8 respective pyridazine, pyrazine and other heteroaryl carboxylic acid esters.  
9 The analogous aryl and heteroaryl hydroxyl compounds and amines,  
10 wherein the halogen of the above-listed compounds is replaced by OH or  $NH_2$   
11 respectively, also serve as additional examples for the reagents of the formula  
12  $X_4-A(R_2)-(CH_2)_n-COOR_8$ . In these examples  $X_4$  is OH or  $NH_2$ , respectively.

13 Still further in accordance with the general synthetic methodology to  
14 provide the compounds of **Formulas 1** through **8** a derivative of the  
15 substituted phenyl, substituted tetrahydronaphthalene, substituted chroman,  
16 thiochroman, tetrahydroquinoline or tetrahydroisoquinoline moiety is  
17 synthesized first, having a covalently attached  $X_5$  group. The  $X_5$  group reacts  
18 with the  $X_4$  group of the reagent  $X_4-A(R_2)-(CH_2)_n-COOR_8$  to form the linker  
19 designated **Z** in **Formulas 1** through **8**. The  $X_5$  group is one that is capable of  
20 participating in a catalyzed coupling reaction, (such as an ethynyl group when  
21  $X_4$  is a leaving group), or a leaving group (such as halogen or  
22 trifluoromethanesulfonyloxy when  $X_4$  is an ethynyl group), or an activated  
23 carboxylic acid function (when  $X_4$  is OH or  $NH_2$ ). The  $X_5$  group can also be  
24 an OH, SH or  $NH_2$  group when the  $X_4$  group is an activated carboxylic acid  
25 function. Specific examples for substituted phenyl, substituted  
26 tetrahydronaphthalene, substituted chroman, thiochroman, tetrahydroquinoline  
27 or tetrahydroisoquinoline intermediates having an  $X_5$  functionality are  
28 provided below, and are also available in the chemical scientific and patent



1 literature. Generally speaking, for reagents and reactions covalently joining a  
2 substituted tetrahydronaphthalene, substituted chroman, thiochroman, or  
3 tetrahydroquinoline intermediate with a substituted aryl or heteroaryl group,  
4 such as  $X_4-A(R_2)-(CH_2)_n-COOR_8$ , to form a compound including the linker  
5 designated **Z**, reference is made to United States Patent Nos. 5,648,503;  
6 5,723,666 and 5,952,345 the specification of each of which are expressly  
7 incorporated herein by reference.

8 The substituted phenyl, tetrahydronaphthalene, chroman, thiochroman,  
9 tetrahydroquinoline or tetrahydroisoquinoline moiety of the novel compounds  
10 used in accordance with the invention are derivatized in a manner to include  
11 the specific substituents (such as for example the cycloalkyl substituents)  
12 encompassed within the scope of the invention, either before or after the -  
13  $A(R_2)-(CH_2)_n-COOR_8$  moiety has been attached and the linker **Z** has formed,  
14 as illustrated by the below described specific examples.

15 The  $-(CH_2)_n-COOR_8$  moiety of the compounds of **Formulas 1** through **8** can  
16 be modified in order to obtain still further novel compounds. One such  
17 modification is saponification of compounds where the  $R_8$  group is an alkyl or  
18  $-CH_2O(C_{1-6}\text{-alkyl})$  group. Another modification is esterification of the  
19 carboxylic acid function when the  $R_8$  group is H or a cation. Such  
20 saponification and esterification reactions are well known in the art and within  
21 the skill of the practicing organic chemist. Still another modification of the  
22 compounds used in accordance with the invention (or of the intermediates  $X_4-$   
23  $A(R_2)-(CH_2)_n-COOR_8$ , or of precursors to these intermediates) is the  
24 homologation of the  $(CH_2)_n$  group. The latter can be accomplished, for  
25 example, by the well known *Arndt-Eistert* method of homologation, or other  
26 known methods of homologation.

27 The previously known compounds which have been discovered to be  
28 inhibitors of cytochrome P450RAI and which are used in accordance with

1 the present invention are made, generally speaking, pursuant to the teachings  
2 of a patent or publication which is identified in connection with each of the  
3 known compounds. These patents or publications are incorporated by  
4 reference in the present specification.

5 The synthetic procedure of homologation that may be utilized for  
6 providing a compound having the partial structure of  $-A(R_2)-(CH_2)_n-COOR_8$   
7 where  $n$  is 1, or 2 (one or two), preferably 1 (one), can be one of the several  
8 known procedures of homologation of carboxylic acids or esters, such as the  
9 *Arndt-Eistert* procedure that is described *inter alia* in March, Advanced  
10 Organic Chemistry: Reactions, Mechanisms, and Structure, pages 809-810,  
11 McGraw-Hill Publishers, 1968, incorporated herein by reference. Alternatively  
12 the homologs of the partial structure of  $-A(R_2)-(CH_2)_n-COOR_8$  are  
13 synthesized in accordance with the synthetic schemes disclosed herein in  
14 connection with the preparation of the novel compounds.

#### 15 SPECIFIC EMBODIMENTS

16 With reference to the symbol **A** in **Formulas 1** through **8**, the preferred  
17 novel compounds used in accordance with the present invention are those  
18 where **A** is phenyl, naphthyl, pyridyl, thienyl or furyl. Even more preferred  
19 are compounds where **A** is phenyl. As far as substitutions on the **A** (phenyl)  
20 and **A** (pyridyl) groups are concerned, compounds are preferred where the  
21 phenyl group is 1,4 (*para*) substituted and where the pyridine ring is 2,5  
22 substituted. (Substitution in the 2,5 positions in the "pyridine" nomenclature  
23 corresponds to substitution in the 6-position in the "nicotinic acid"  
24 nomenclature.) In the presently preferred novel compounds used in  
25 accordance with the invention either there is no  $R_2$  substituent on the **A** group,  
26 or the  $R_2$  substituent is preferably a fluoro group that is preferably located on  
27 the aromatic carbon adjacent (*ortho*) to the carbon bearing the  $-(CH_2)_n-$   
28  $COOR_8$  group.

1 As far as the  $-(CH_2)_n-COOR_8$  is concerned the use of novel  
2 compounds is preferred where  $n$  is 0, 1 or 2, and even more preferred where  $n$   
3 is 1. In **Formulas 5 and 8** only compounds where  $n$  is 1 or 2 are preferred,  
4 with  $n=1$  being most preferred. For the  $R_8$  group H, lower alkyl of 1 to 3  
5 carbons, and  $-CH_2O(C_{1-6}\text{-alkyl})$  groups are preferred, as well as the  
6 pharmaceutically acceptable salts of the free acids when  $R_8$  is H. Among the  
7 lower alkyl and  $-CH_2O(C_{1-6}\text{-alkyl})$  groups ethyl and  $OCH_2CH_3$ , respectively,  
8 are presently most preferred.

9 The linker group  $Z$  in all of the novel compounds used in accordance  
10 with the invention is preferably ethynyl  
11  $(-C\equiv C-)$ , ester  $(CO-O)$ , ethenyl,  $(-CR_1=CR_1-)$  or amide  $(CONR_1)$ . Among  
12 these the ethynyl  $(-C\equiv C-)$  and ester  $(CO-O)$  linkers are most preferred.  
13 Moreover, preferably the linker  $Z$  is attached to the 6 position in **Formula 1**,  
14 to the 4 position in **Formula 2**, to the 6 position in **Formula 3**, to the 6  
15 position in **Formula 4**, to the 4 position in **Formula 5**, to the 4 position in  
16 **Formula 6**, to the 6 position in **Formula 7**, and to the 6 position in **Formula**  
17 **8**. These positions are indicated by arabic numerals in **Formulas 1 through 8**.

18 The  $R_1$  group substituting the non-aromatic rings in **Formulas 1, 3, 4, 7**  
19 and **8** is preferably alkyl, more preferably alkyl of 1 to 3 carbons, and most  
20 preferably methyl. The  $R_1$  group substituting the cyclopropane ring in  
21 **Formulas 1, 2, 3 and 7** is preferably non-existent ( $p$  is 0), or is alkyl of 1 to 3  
22 carbons, even more preferably methyl.

23 The  $X$  group in **Formulas 1 and 5** is preferably O, and in **Formula 2**  $X$   
24 is preferably O or NR.

25 The  $X_1$  group in **Formula 4** is preferably 1-imidazolyl, substituted 1-  
26 imidazolyl, or  $NRR_6$ , where  $R_6$  is preferably cyclopropyl or branched-chain  
27 alkyl. The  $X_2$  group in **Formula 6** is preferably 1-imidazolyl or substituted  
28 1-imidazolyl.

1           The  $X_3$  group in **Formula 8** is preferably O or C=O.

2           The Y group is preferably H, lower alkyl of 1 to 3 carbons, cycloalkyl,  
3 lower alkyl substituted cycloalkyl, or halogen. Among these, H, Cl, and  
4 cyclopropyl are most preferred.

5           The  $Y_1$  group of **Formula 8** is preferably H, lower alkyl of 1 to 3  
6 carbons, cycloalkyl, or lower alkyl substituted cycloalkyl. Among these H,  
7 ethyl and cyclopropyl are presently most preferred.

8           The most preferred novel compounds used in accordance with the  
9 invention are disclosed in **Tables 2** through **9** with reference to **Formulas 9**  
10 through **16**. The compounds specifically shown in **Tables 2** through **9** are  
11 carboxylic acids, but it should be understood that the use of the corresponding  
12  $C_{1-3}$ alkyl esters, methoxymethyl ( $OCH_2CH_3$ ) esters and of pharmaceutically  
13 acceptable salts of the acids shown in these tables is also highly preferred.

14           It should also be apparent that the preferred compounds shown in **Table**  
15 **2** with reference to the more specific **Formula 9** are within the scope of  
16 **Formula 1**.

17           Similarly, the preferred compounds shown in **Table 3** with reference to  
18 the more specific **Formula 10** are within the scope of **Formula 2**;

19           the preferred compounds shown in **Table 4** with reference to the more  
20 specific **Formula 11** are within the scope of **Formula 3**;

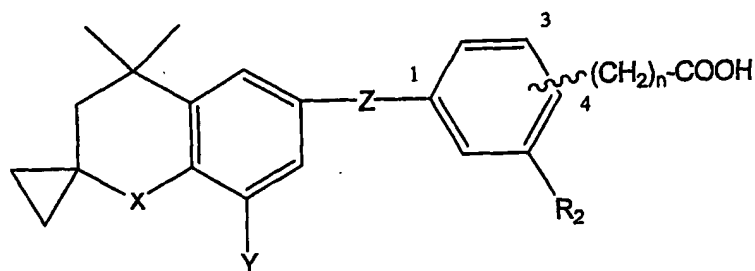
21           the preferred compounds shown in **Table 5** with reference to the more  
22 specific **Formula 12** are within the scope of **Formula 4**;

23           the preferred compounds shown in **Table 6** with reference to the more  
24 specific **Formula 13** are within the scope of **Formula 5**;

25           the preferred compounds shown in **Table 7** with reference to the more  
26 specific **Formula 14** are within the scope of **Formula 6**;

27           the preferred compounds shown in **Table 8** with reference to the more  
28 specific **Formula 15** are within the scope of **Formula 7**, and

the preferred compounds shown in Table 9 with reference to the more specific Formula 16 are within the scope of Formula 8.

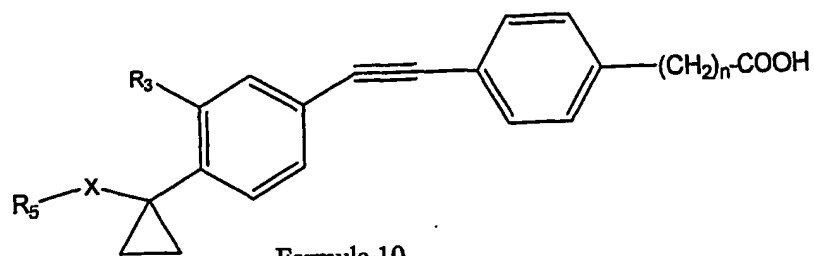


Formula 9

TABLE 2

Compound No.	X	Y	Z	R <sub>2</sub>	n	Position of (CH <sub>2</sub> ) <sub>n</sub> COOH
40	O	H	-C≡C-	H	0	4
42	O	H	-C≡C-	H	1	4
44	O	H	-C≡C-	F	0	4
48	O	cyclopropyl	-C≡C-	H	1	4
50	O	cyclopropyl	-C≡C-	F	1	4
52	O	cyclopropyl	-C≡C-	H	0	4
54	O	cyclopropyl	-C≡C-	F	0	4
58	O	cyclopropyl	-CO-O-	H	1	4
60	O	cyclopropyl	-CO-O-	H	1	3
66	CH <sub>3</sub> N	H	-C≡C-	H	0	4

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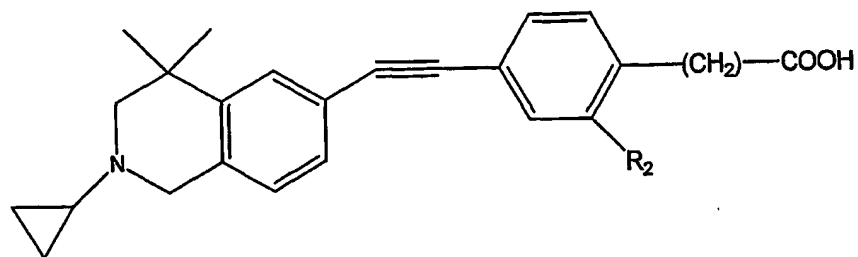
Formula 10

TABLE 3

Compound No.	$R_5$	X	$R_3$	n
110	n-propyl	(n-propyl)N	H	0
112	benzyl	NH	H	0
114	benzyl	(n-benzyl)N	H	0
108	n-propyl	NH	H	0
116	benzyl	methylN	H	0
77	benzyl	O	H	0
78	benzyl	O	H	1
70	methyl	O	H	1
69	methyl	O	H	0
73	isopropyl	O	H	0
74	isopropyl	O	H	1
82	benzyl	O	methyl	1
81	benzyl	O	methyl	0
89	$(CH_3)_3C-CH_2-$	O	methyl	0
90	$(CH_3)_3C-CH_2-$	O	methyl	1
94	benzyl	O	ethyl	1
93	benzyl	O	ethyl	0

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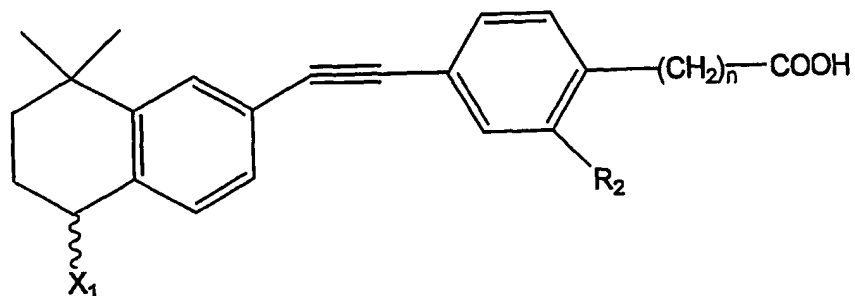
86	isopropyl	O	methyl	1
85	isopropyl	O	methyl	0
105	ethyl	O	<i>t</i> -butyl	0
106	ethyl	O	<i>t</i> -butyl	1
98	isopropyl	O	ethyl	1



Formula 11

TABLE 4

Compound No.	R <sub>2</sub>
22	F
24	H

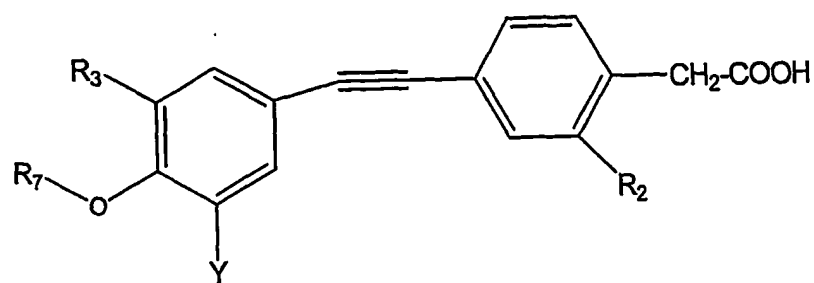


Formula 12

TABLE 5

Compound No.	$X_1$	$R_2$	n
3	methyl,cyclopropyl-N	H	0
8	methyl,cyclopropyl-N	H	1
13	methyl,cyclopropyl-N	F	0
18	methyl,cyclopropyl-N	F	1
139	1-imidazolyl	H	0
137	1-imidazolyl	H	1
26	methyl,isopropyl-N	H	0

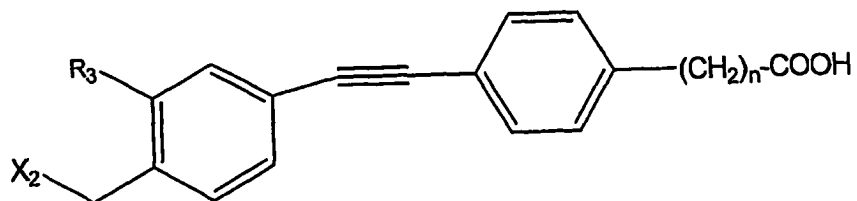




Formula 13

TABLE 6

Compound No.	$R_2$	$R_7$	Y	$R_3$
143	H	methyl	<i>t</i> -butyl	<i>t</i> -butyl
145	F	methyl	<i>t</i> -butyl	<i>t</i> -butyl



Formula 14

TABLE 7

Compound No.	$X_2$	$R_3$	n
119	1-imidazolyl	methyl	0
121	1-imidazolyl	methyl	1
127	1-imidazolyl	iso-propyl	1
126	1-imidazolyl	iso-propyl	0
134	ethyl,cyclopropyl-N	iso-propyl	0
130	ethyl,cyclopropyl-N	methyl	0
131	ethyl,cyclopropyl-N	methyl	1
141	(1-methyl)cyclopropyl-oxy	iso-propyl	1

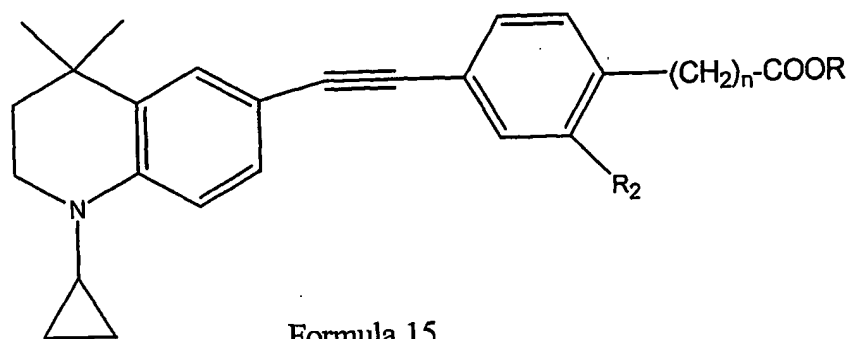
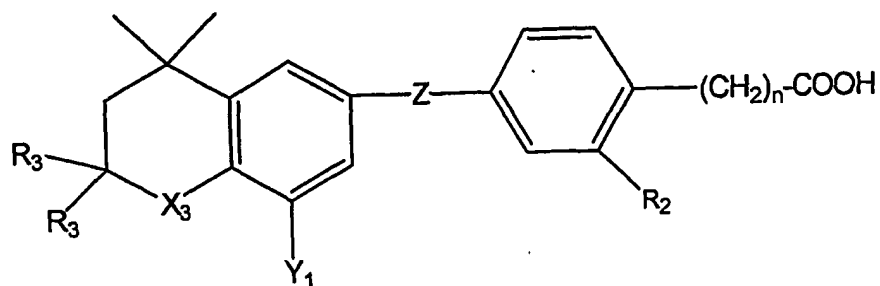


TABLE 8

Compound No.	R	R <sub>2</sub>	n
62	H	H	0
63	Me	H	1



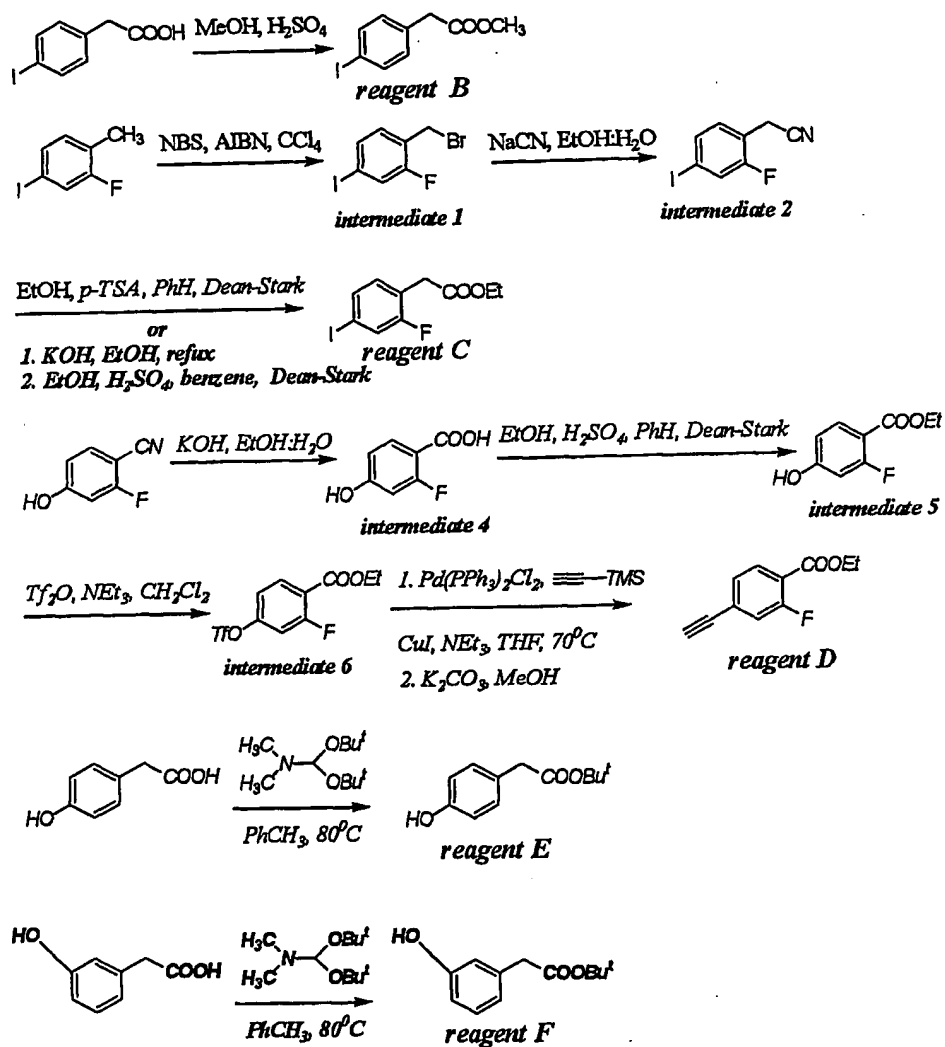
Formula 16

TABLE 9

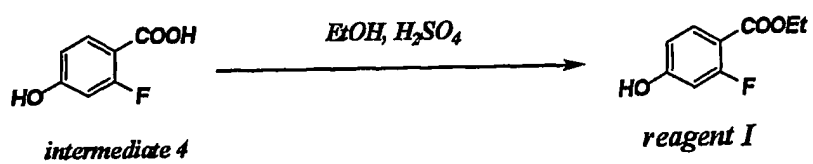
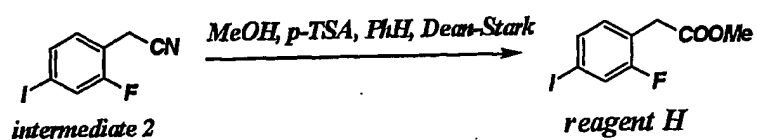
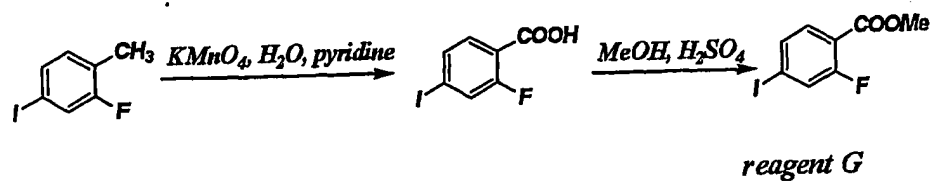
Compound No.	X <sub>3</sub>	Y <sub>1</sub>	R <sub>3</sub>	Z	R <sub>2</sub>	n
28	O	H	methyl	-C≡C-	H	1
30	O	H	methyl	-C≡C-	F	0
5	CO	H	H	-C≡C-	H	1
10	CO	H	H	-C≡C-	F	0
36	O	cyclopropyl	methyl	-C≡C-	H	1
38	O	cyclopropyl	methyl	-C≡C-	F	1
46	O	H	methyl	-CO-O-	H	1
20	CO	H	H	-CO-O-	H	1
32	O	H	methyl	-C≡C-	F	1
56	O	ethyl	methyl	-C≡C-	H	1
34	O	cyclopropyl	methyl	-C≡C-	H	0
15	CO	H	H	-C≡C-	F	1

1       The compounds used in accordance with the invention can be  
2 synthesized by applying the general synthetic methodology described above,  
3 and by such modifications of the hereinafter described specific synthetic routes  
4 which will become readily apparent to the practicing synthetic organic chemist  
5 in light of this disclosure and in view of general knowledge available in the  
6 art. The hereinafter disclosed specific reaction schemes are directed to the  
7 synthesis of exemplary and preferred compounds used in accordance with the  
8 invention. Whereas each of the specific and exemplary synthetic routes shown  
9 in these schemes may describe specific compounds only within the scope of  
10 one or two of the general **Formulas 1 through 8**, the synthetic processes and  
11 methods used therein are adaptable within the skill of the practicing organic  
12 chemist and can be used with such adaptation for the synthesis of compounds  
13 used in accordance with the invention which are not specifically described  
14 herein as examples.

15       **Reaction Scheme 1** discloses a presently preferred synthetic route to  
16 certain intermediates or reagents having the general formula  $X_4-A(R_2)-CH_2)_n-$   
17  $COOR_g$ , where the symbol **A** represents a di-, or tri-substituted phenyl  
18 moiety. These intermediates are utilized in the synthesis of the novel  
19 compounds used in accordance with the invention.



REACTION SCHEME 1



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REACTION SCHEME 1 CONTINUED

1        **Reaction Scheme 2** discloses presently preferred synthetic routes to  
2 obtain exemplary and preferred novel tetrahydronaphthalenone compounds  
3 within the scope of **Formula 8** where the symbol  $X_3$  represents a C=O  
4 group, **Z** represents an ethynyl moiety or a -COO- (ester) function, and **A** is a  
5 substituted phenyl moiety.

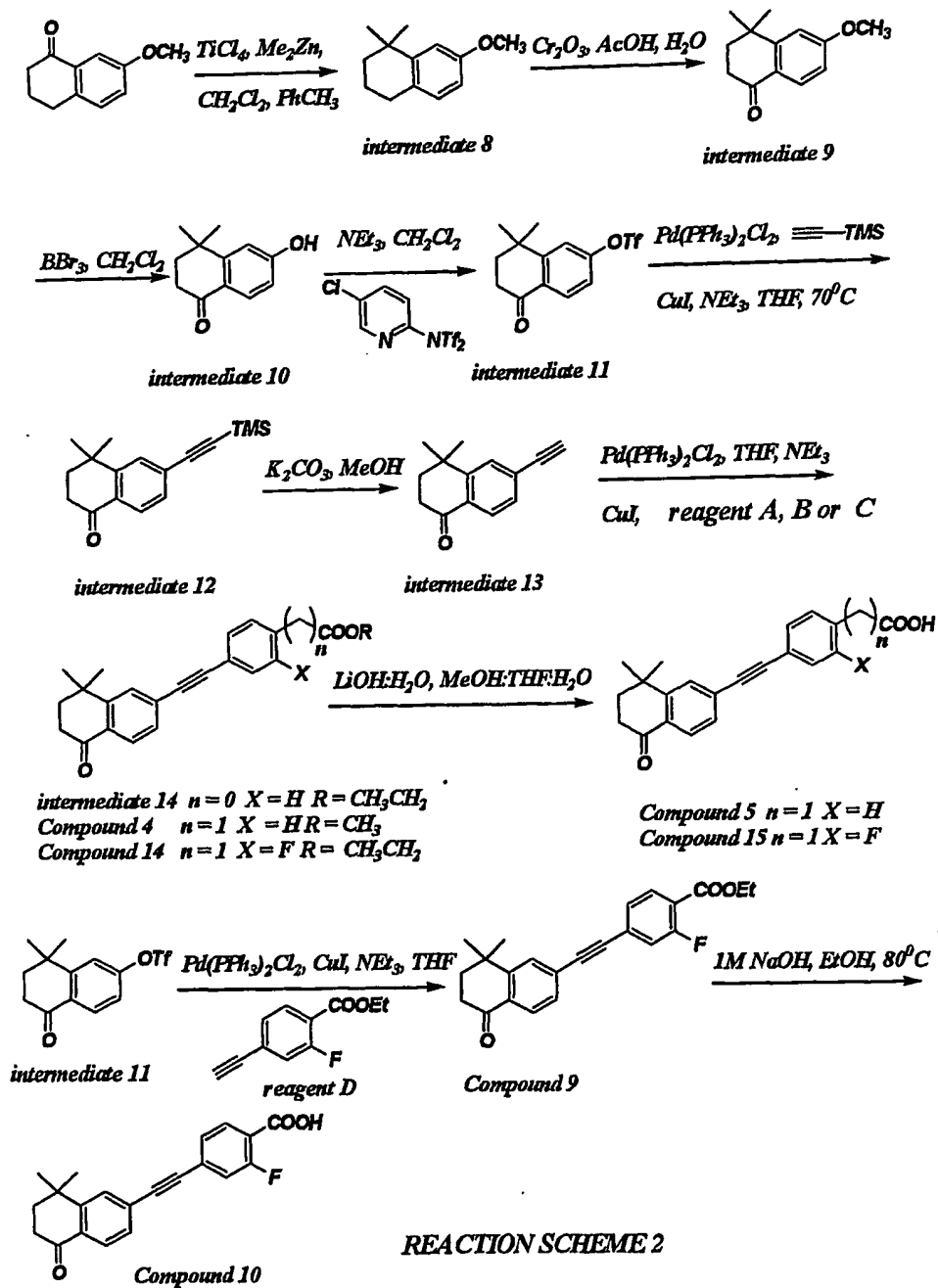
6        **Reaction Scheme 3** discloses presently preferred synthetic routes to  
7 obtain exemplary and preferred novel tetrahydronaphthalene compounds  
8 within the scope of **Formula 4** where  $X_1$  represents a dialkyl substituted  
9 nitrogen, **Z** is an ethynyl moiety and **A** is a substituted phenyl moiety.

10       **Reaction Scheme 4** discloses presently preferred synthetic routes to  
11 obtain exemplary and preferred novel isoquinoline compounds within the  
12 scope of **Formula 3** where the symbol **Y** represents hydrogen, **Z** is an  
13 ethynyl moiety and **A** is a substituted phenyl moiety.

14       **Reaction Scheme 5** discloses presently preferred synthetic routes to  
15 obtain exemplary and preferred novel chroman compounds within the scope of  
16 **Formula 8** where the symbol  $Y_1$  represents hydrogen, **Z** is an ethynyl moiety  
17 or an ester (COO) function, and **A** is a substituted phenyl moiety.



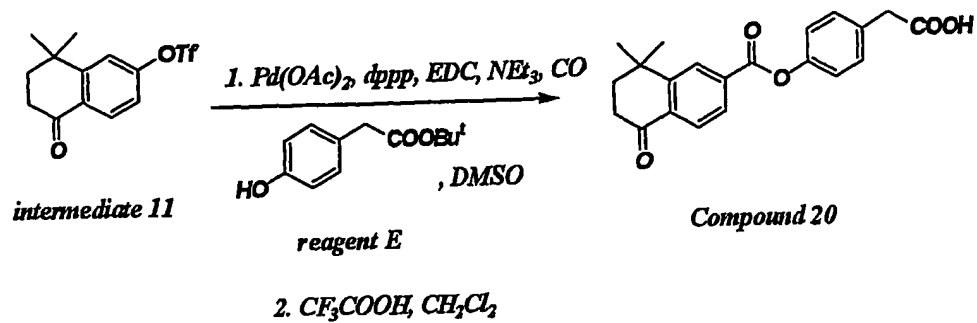
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**REACTION SCHEME 2 CONTINUED**

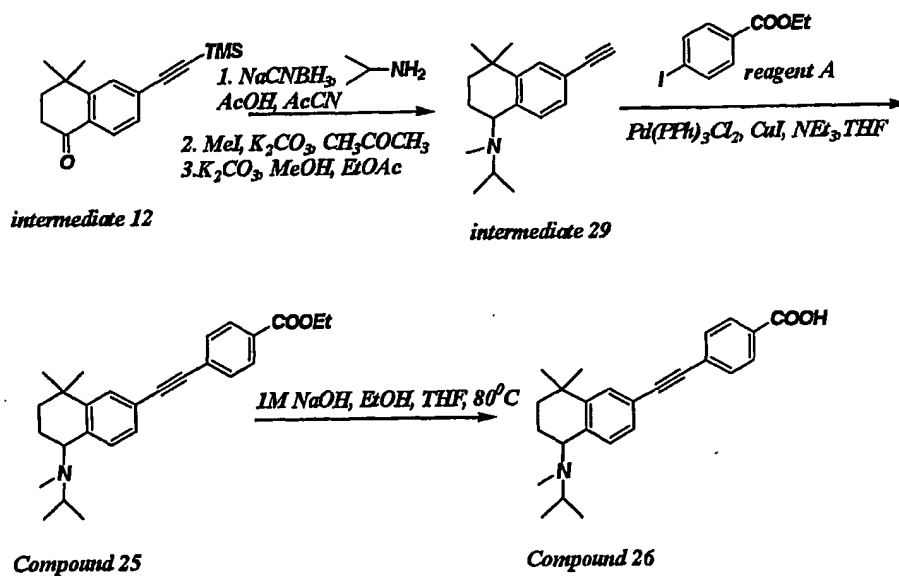
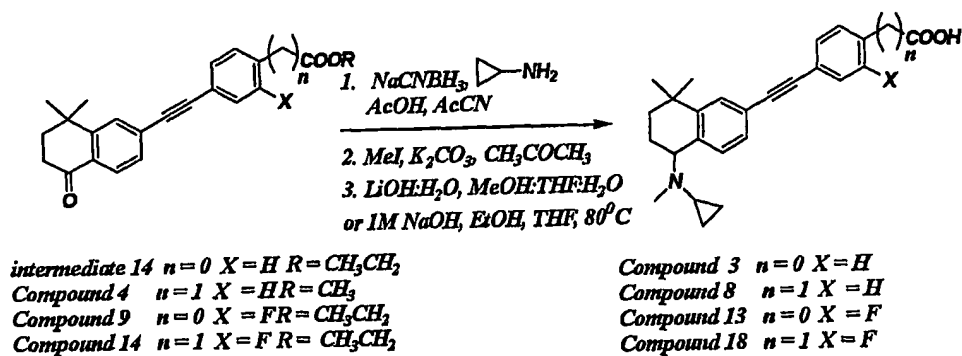
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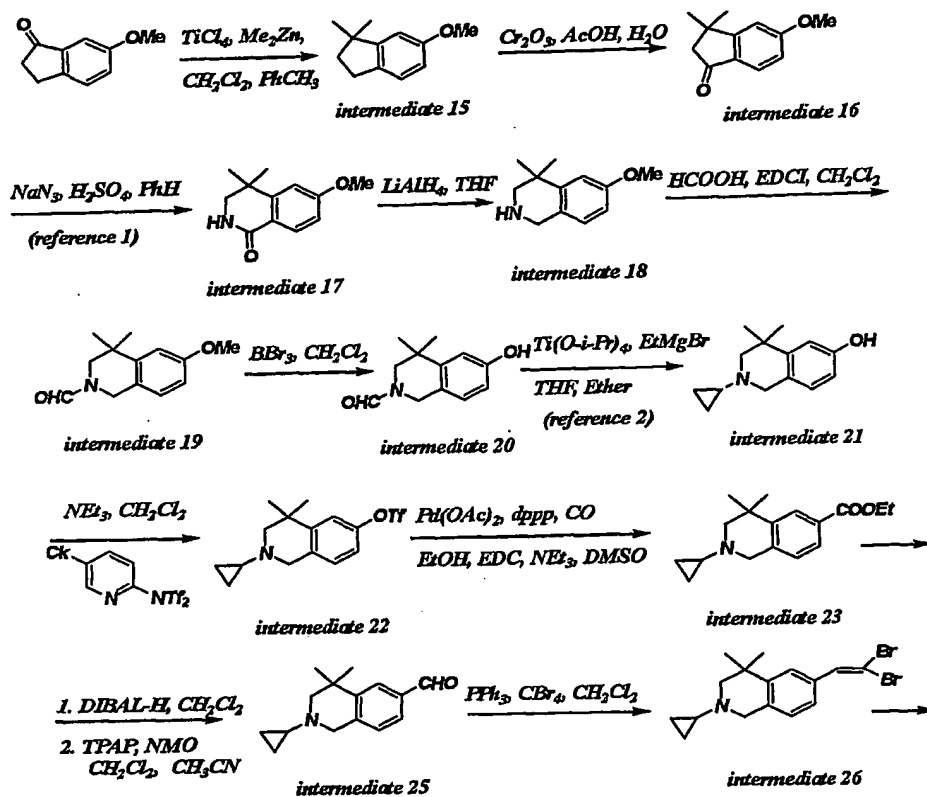
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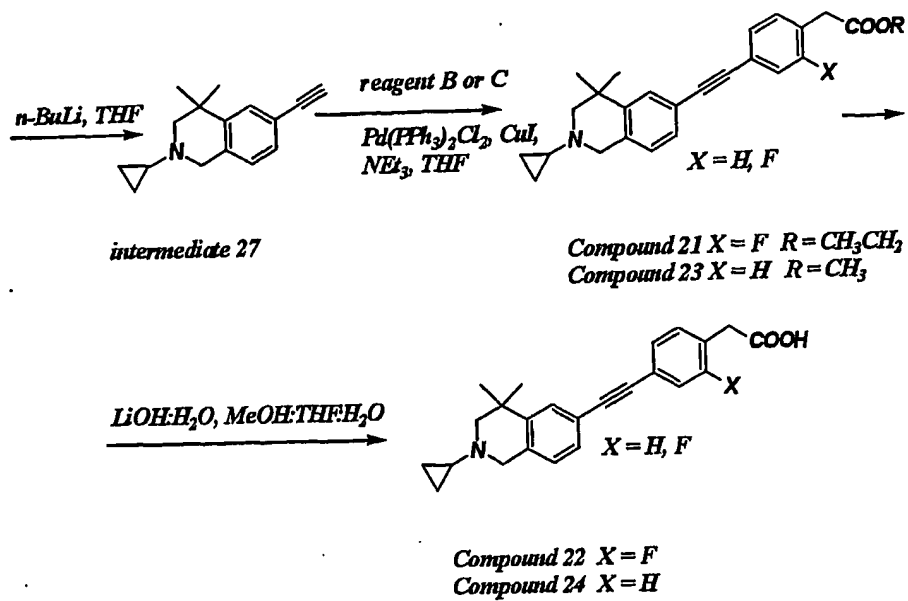
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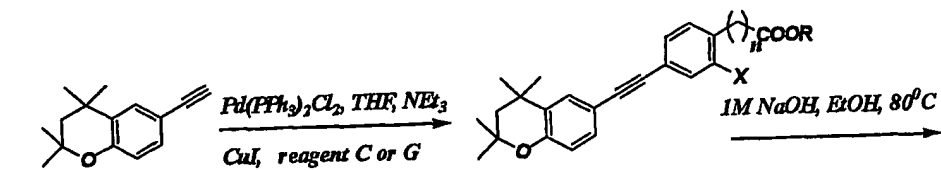
REACTION SCHEME 3





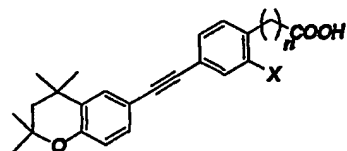
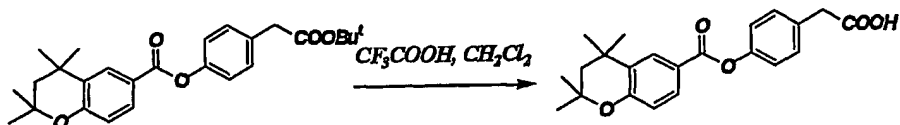
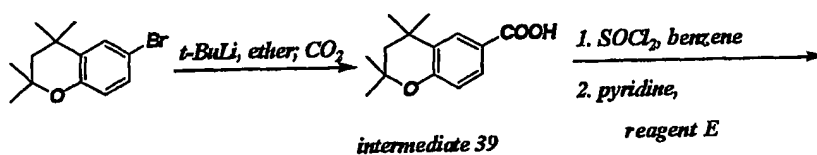
## REACTION SCHEME 4 CONTINUED

1



U. S. Patent Nos. 5,045,551 and 5,616,597

Compound 29  $X = \text{F } n = 0 \text{ } R = \text{CH}_3$   
 Compound 31  $X = \text{F } n = 1 \text{ } R = \text{CH}_2\text{CH}_3$

Compound 30  $X = \text{F } n = 0$ Compound 32  $X = \text{F } n = 1$ 

Compound 45

Compound 46

## REACTION SCHEME 5

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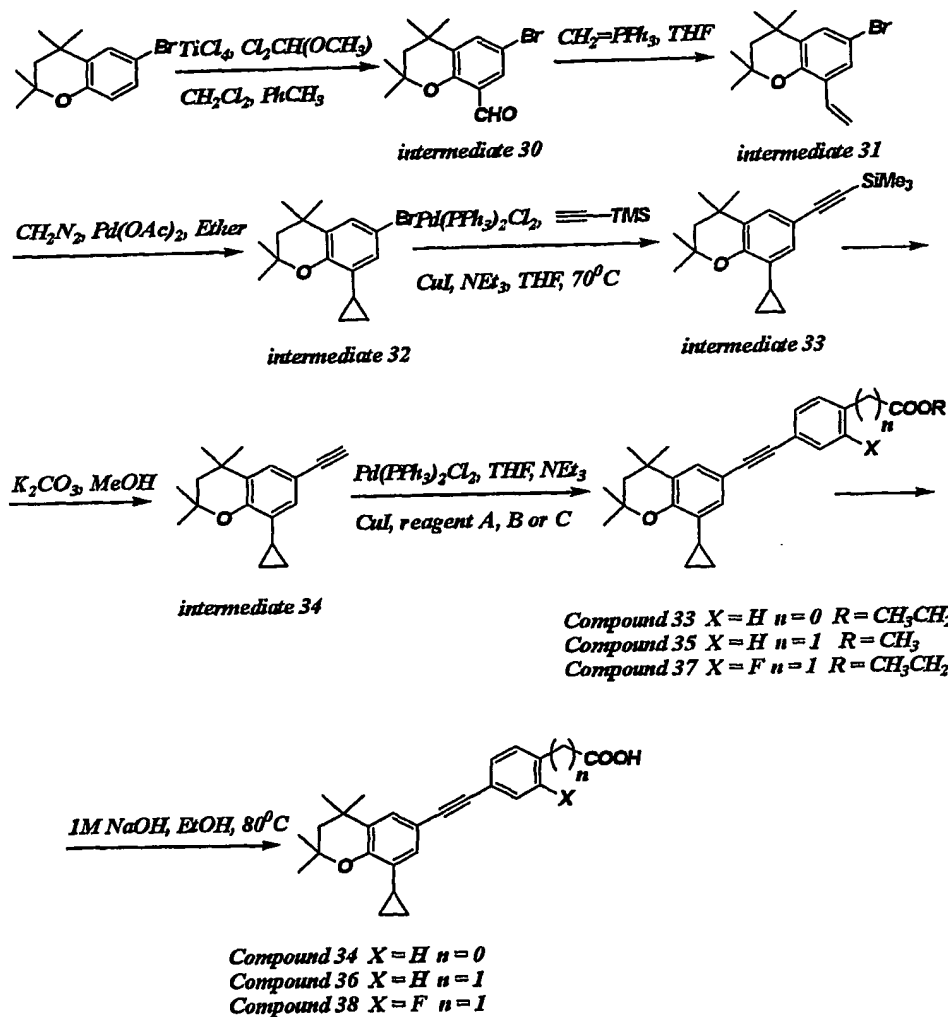
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7

1        **Reaction Scheme 6** discloses presently preferred synthetic routes to  
2 obtain other exemplary and preferred novel chroman compounds within the  
3 scope of **Formula 8** where the symbol  $Y_1$  represents a cyclopropyl group, **Z**  
4 is an ethynyl moiety and **A** is a substituted phenyl moiety.

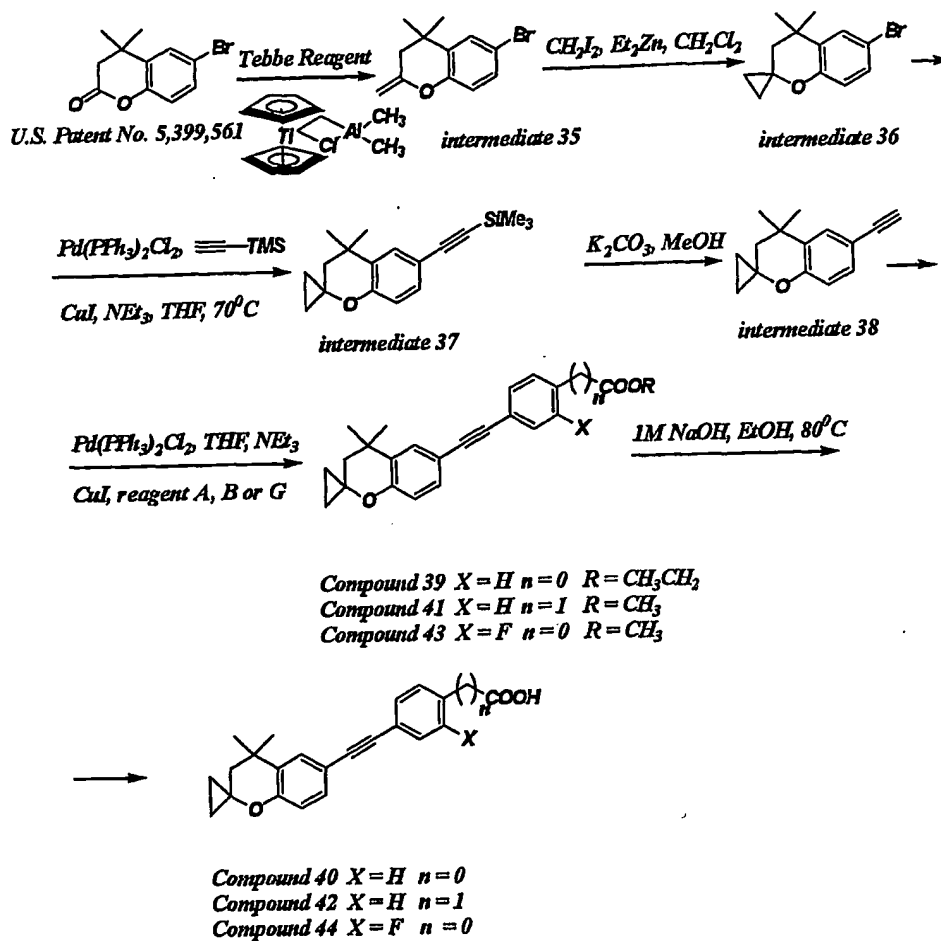
5        **Reaction Scheme 7** discloses presently preferred synthetic routes to  
6 obtain exemplary and preferred novel chroman compounds within the scope of  
7 **Formula 1** where the symbol **X** represents oxygen (O), **Y** represents  
8 hydrogen, **Z** is an ethynyl moiety and **A** is a substituted phenyl moiety.

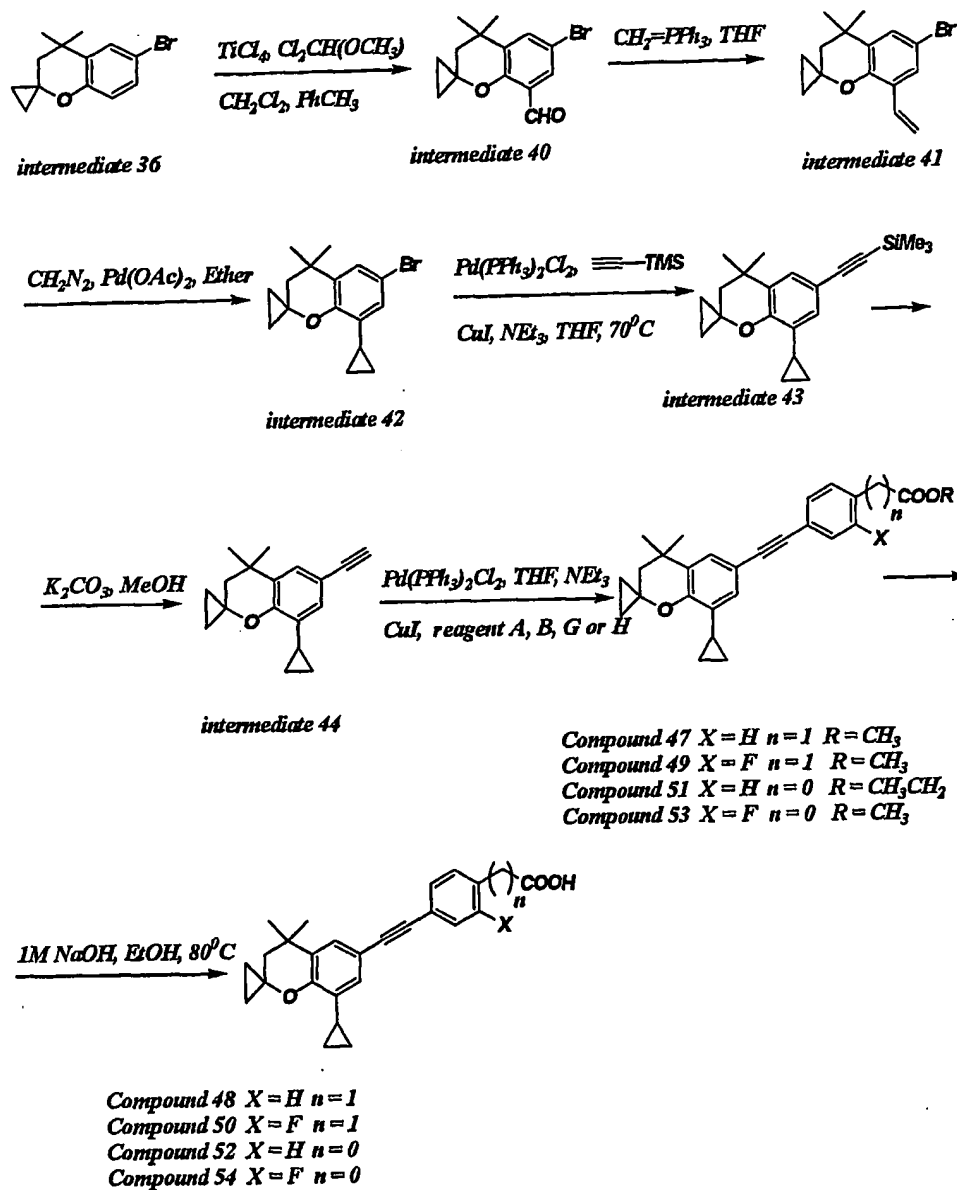
9        **Reaction Scheme 8** discloses presently preferred synthetic routes to  
10 obtain other exemplary and preferred novel chroman compounds within the  
11 scope of **Formula 1** where the symbol **X** represents oxygen (O), **Y** represents  
12 a cyclopropyl group, **Z** is an ethynyl moiety and **A** is a substituted phenyl  
13 moiety.



REACTION SCHEME 6







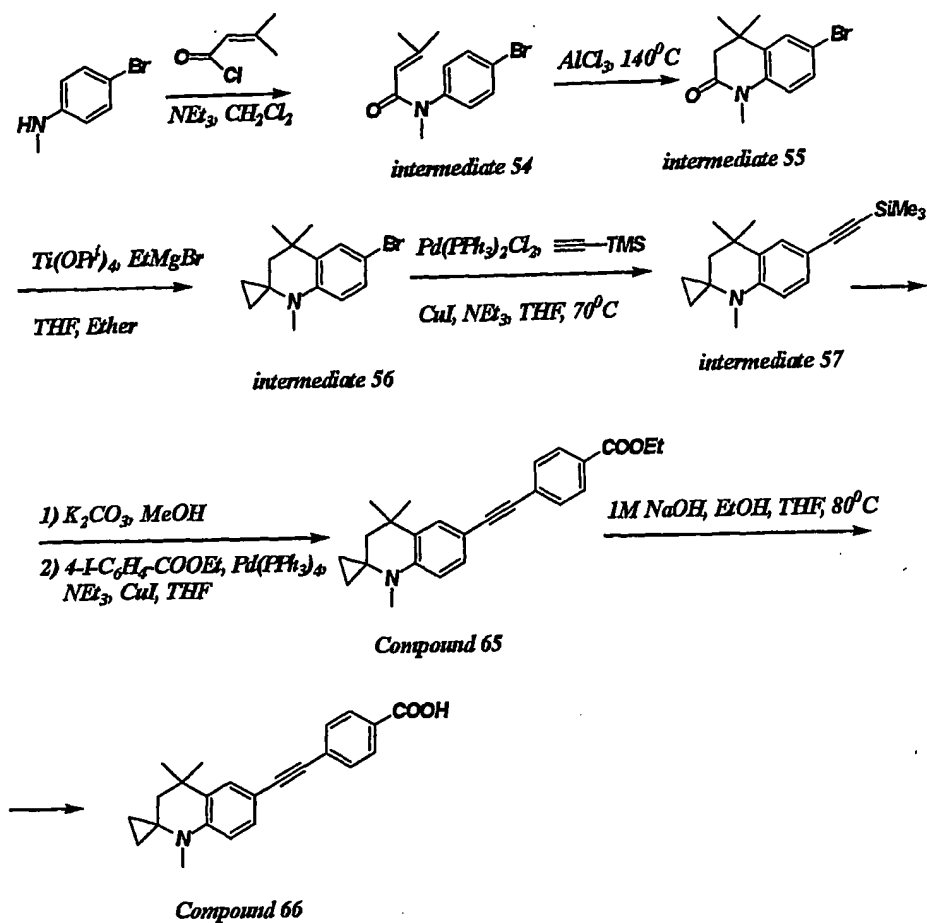
REACTION SCHEME 8

1        **Reaction Scheme 9** discloses presently preferred synthetic routes to  
2 obtain exemplary and preferred novel tetrahydroquinoline compounds within  
3 the scope of **Formula 1** where the symbol **X** represents an alkyl substituted  
4 nitrogen (alkyl-N), **Y** represents hydrogen, **Z** is an ethynyl moiety and **A** is a  
5 substituted phenyl moiety.

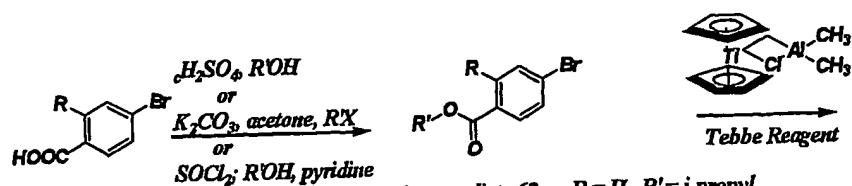
6        **Reaction Schemes 10 and 11** disclose presently preferred synthetic  
7 routes to obtain exemplary and preferred novel phenyl compounds within the  
8 scope of **Formula 2** where the symbol **X** represents oxygen (O), **R<sub>5</sub>** is alkyl or  
9 benzyl, **Z** is an ethynyl moiety and **A** is a substituted phenyl moiety.

10       **Reaction Scheme 12** discloses presently preferred synthetic routes to  
11 obtain exemplary and preferred novel phenyl compounds within the scope of  
12 **Formula 2** where the symbol **R<sub>5</sub>-X** represents an alkyl, dialkyl, benzyl or  
13 dibenzyl substituted nitrogen, **Z** is an ethynyl moiety and **A** is a substituted  
14 phenyl moiety.

15       **Reaction Schemes 13 and 14** disclose presently preferred synthetic  
16 routes to obtain exemplary and preferred novel phenyl compounds within the  
17 scope of **Formula 6** where the symbol **X<sub>2</sub>** represents a (1-imidazolyl) moiety,  
18 **Z** is an ethynyl moiety and **A** is a substituted phenyl moiety.

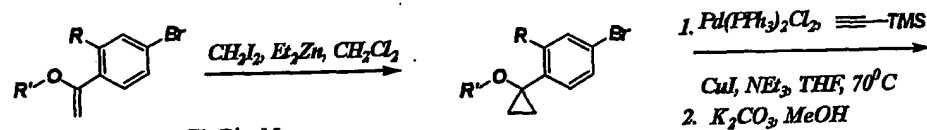


REACTION SCHEME 9



$R = H, Me, Et$

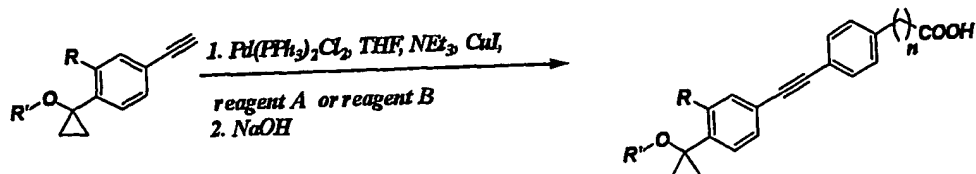
intermediate 62  $R = H$   $R' = i\text{-propyl}$   
 intermediate 67  $R = H$   $R' = \text{benzyl}$   
 intermediate 72  $R = Me$   $R' = \text{benzyl}$   
 intermediate 77  $R = Me$   $R' = i\text{-propyl}$   
 intermediate 82  $R = Me$   $R' = \text{neopentyl}$   
 intermediate 86  $R = Et$   $R' = \text{benzyl}$   
 intermediate 91  $R = Et$   $R' = i\text{-propyl}$



intermediate 58  $R = H$   $R' = Me$   
 intermediate 63  $R = H$   $R' = i\text{-propyl}$   
 intermediate 68  $R = H$   $R' = \text{benzyl}$   
 intermediate 73  $R = Me$   $R' = \text{benzyl}$   
 intermediate 78  $R = Me$   $R' = i\text{-propyl}$   
 intermediate 83  $R = Me$   $R' = \text{neopentyl}$   
 intermediate 87  $R = Et$   $R' = \text{benzyl}$   
 intermediate 92  $R = Et$   $R' = i\text{-propyl}$

intermediate 59  $R = H$   $R' = Me$   
 intermediate 64  $R = H$   $R' = i\text{-propyl}$   
 intermediate 69  $R = H$   $R' = \text{benzyl}$   
 intermediate 74  $R = Me$   $R' = \text{benzyl}$   
 intermediate 79  $R = Me$   $R' = i\text{-propyl}$   
 intermediate 84  $R = Me$   $R' = \text{neopentyl}$   
 intermediate 88  $R = Et$   $R' = \text{benzyl}$   
 intermediate 93  $R = Et$   $R' = i\text{-propyl}$

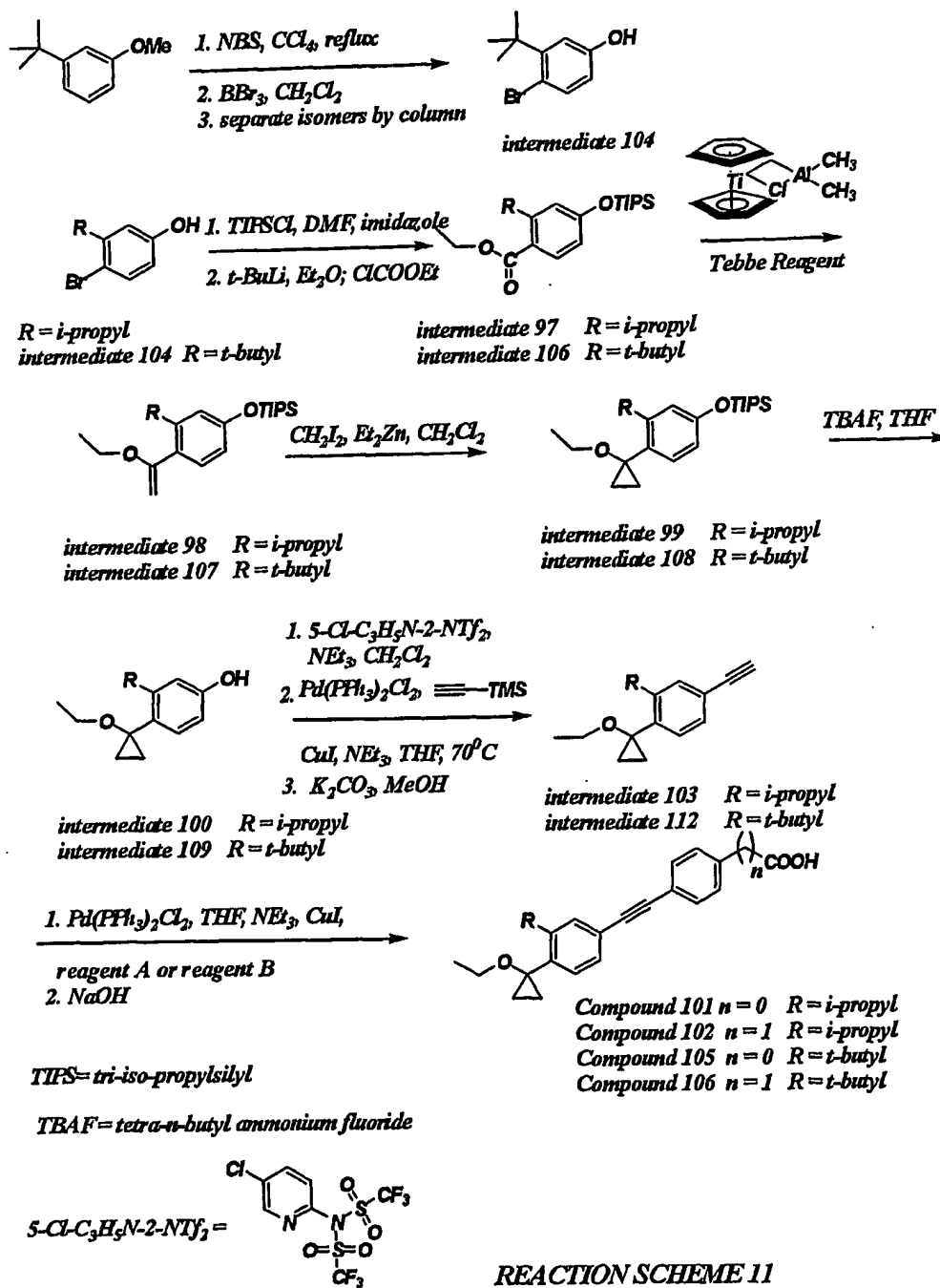
## REACTION SCHEME 10

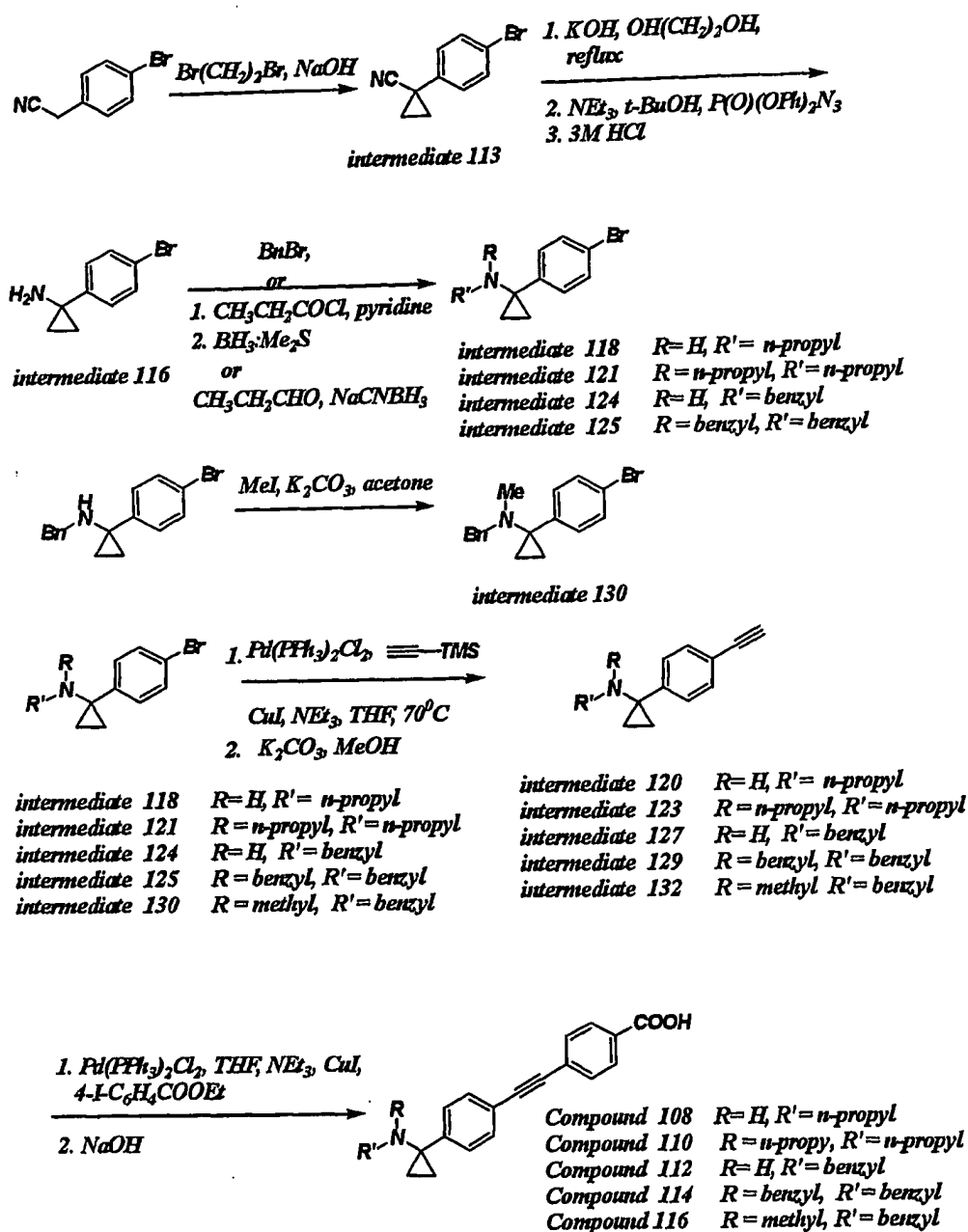


intermediate 61  $R=\text{H}$   $R'=\text{Me}$   
 intermediate 66  $R=\text{H}$   $R'=\text{i-propyl}$   
 intermediate 71  $R=\text{H}$   $R'=\text{benzyl}$   
 intermediate 76  $R=\text{Me}$   $R'=\text{benzyl}$   
 intermediate 81  $R=\text{Me}$   $R'=\text{i-propyl}$   
 intermediate 85  $R=\text{Me}$   $R'=\text{neopentyl}$   
 intermediate 90  $R=\text{Et}$   $R'=\text{benzyl}$   
 intermediate 95  $R=\text{Et}$   $R'=\text{i-propyl}$

Compound 69  $n=0$   $R=\text{H}$   $R'=\text{methyl}$   
 Compound 70  $n=1$   $R=\text{H}$   $R'=\text{methyl}$   
 Compound 73  $n=0$   $R=\text{H}$   $R'=\text{i-propyl}$   
 Compound 74  $n=1$   $R=\text{H}$   $R'=\text{i-propyl}$   
 Compound 77  $n=0$   $R=\text{H}$   $R'=\text{benzyl}$   
 Compound 78  $n=1$   $R=\text{H}$   $R'=\text{benzyl}$   
 Compound 81  $n=0$   $R=\text{Me}$   $R'=\text{benzyl}$   
 Compound 82  $n=1$   $R=\text{Me}$   $R'=\text{benzyl}$   
 Compound 85  $n=0$   $R=\text{Me}$   $R'=\text{i-propyl}$   
 Compound 86  $n=1$   $R=\text{Me}$   $R'=\text{i-propyl}$   
 Compound 89  $n=0$   $R=\text{Me}$   $R'=\text{neopentyl}$   
 Compound 90  $n=1$   $R=\text{Me}$   $R'=\text{neopentyl}$   
 Compound 93  $n=0$   $R=\text{Et}$   $R'=\text{benzyl}$   
 Compound 94  $n=1$   $R=\text{Et}$   $R'=\text{benzyl}$   
 Compound 97  $n=0$   $R=\text{Et}$   $R'=\text{i-propyl}$   
 Compound 98  $n=1$   $R=\text{Et}$   $R'=\text{i-propyl}$

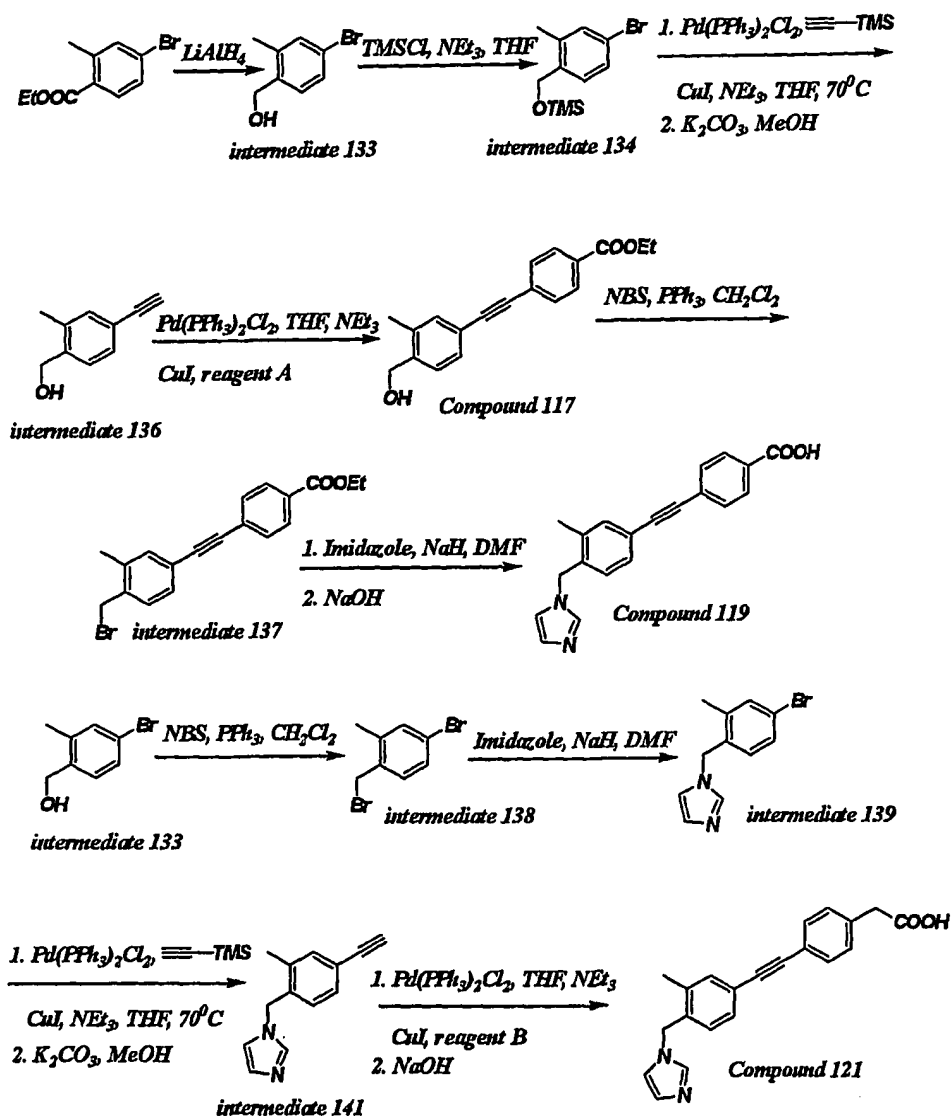
## REACTION SCHEME 10 CONTINUED



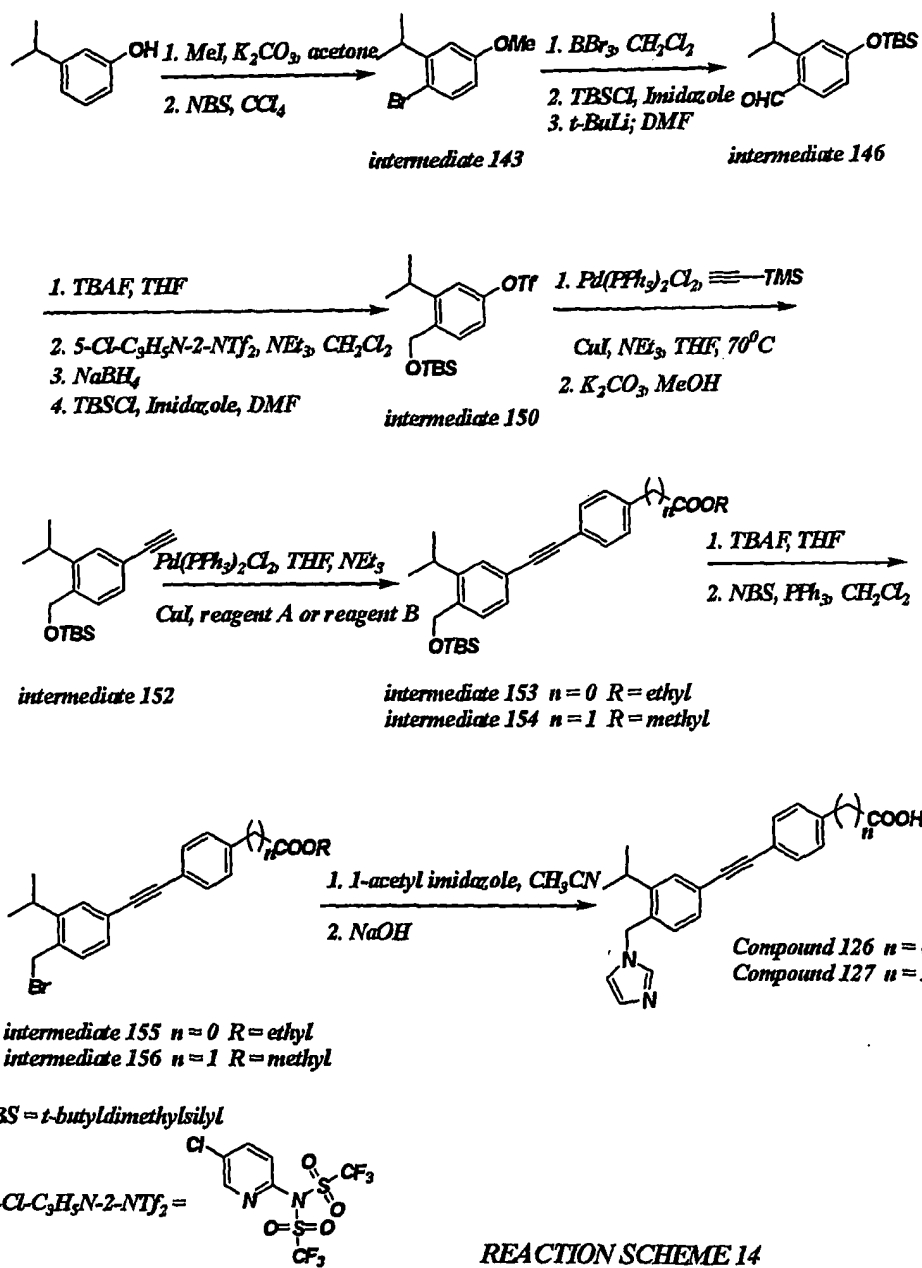


REACTION SCHEME 12





REACTION SCHEME 13



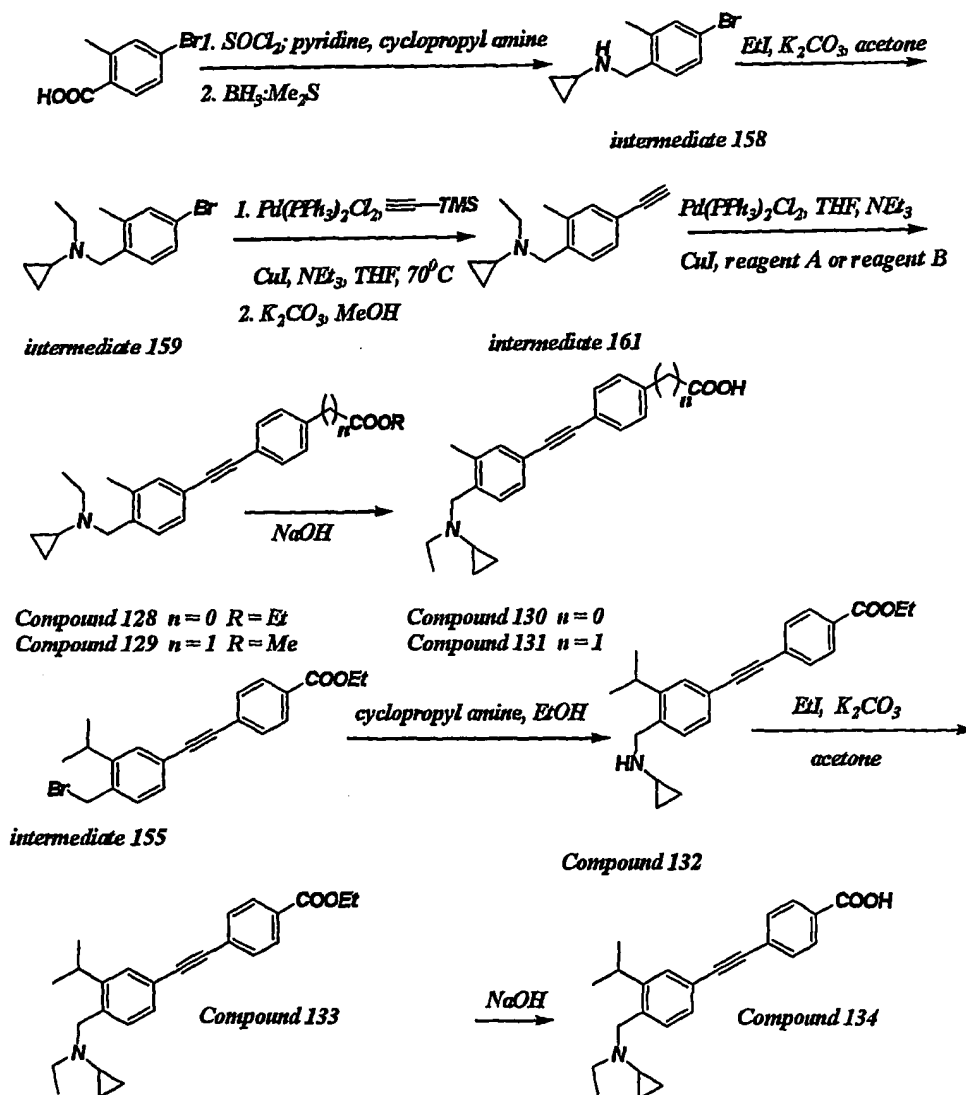
1           **Reaction Scheme 15** disclose presently preferred synthetic routes to  
2 obtain exemplary and preferred novel phenyl compounds within the scope of  
3 **Formula 6** where  $X_2$  represents an alkyl and cyclopropyl substituted nitrogen  
4 ( $X_2 = (\text{alkyl, cycloalkyl})N$ ),  $Y$  represents hydrogen,  $Z$  is an ethynyl moiety  
5 and  $A$  is a substituted phenyl moiety.

6           **Reaction Scheme 16** discloses presently preferred synthetic routes to  
7 obtain exemplary and preferred novel tetrahydronaphthalene compounds  
8 within the scope of **Formula 4** where the symbol  $X_1$  represents a (1-  
9 imidazolyl) moiety,  $Y$  represents hydrogen,  $Z$  is an ethynyl moiety and  $A$  is a  
10 substituted phenyl moiety.

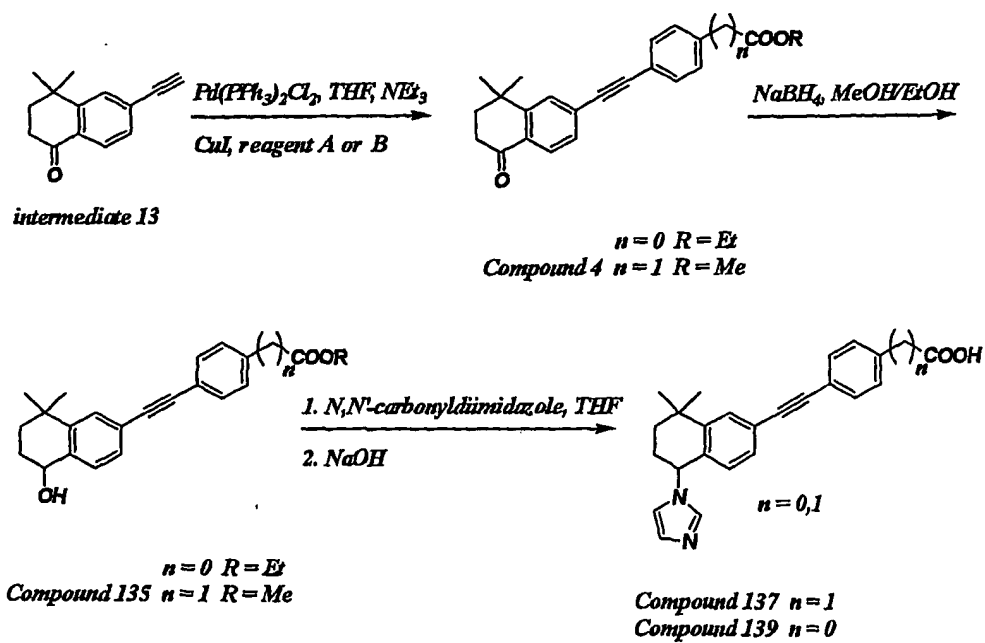
11           **Reaction Scheme 17** discloses presently preferred synthetic routes to  
12 obtain exemplary and preferred novel phenyl compounds within the scope of  
13 **Formula 6** where the symbol  $X_2$  represents a 1-methyl-cyclopropoxy moiety,  
14  $Y$  represents hydrogen,  $Z$  is an ethynyl moiety and  $A$  is a substituted phenyl  
15 moiety.

16           **Reaction Scheme 18** discloses presently preferred synthetic routes to  
17 obtain exemplary and preferred novel phenyl compounds within the scope of  
18 **Formula 5** where the symbol  $X$  represents oxygen (O),  $Y$  represents a  
19 *tertiary*-butyl group,  $Z$  is an ethynyl moiety and  $A$  is a substituted phenyl  
20 moiety.

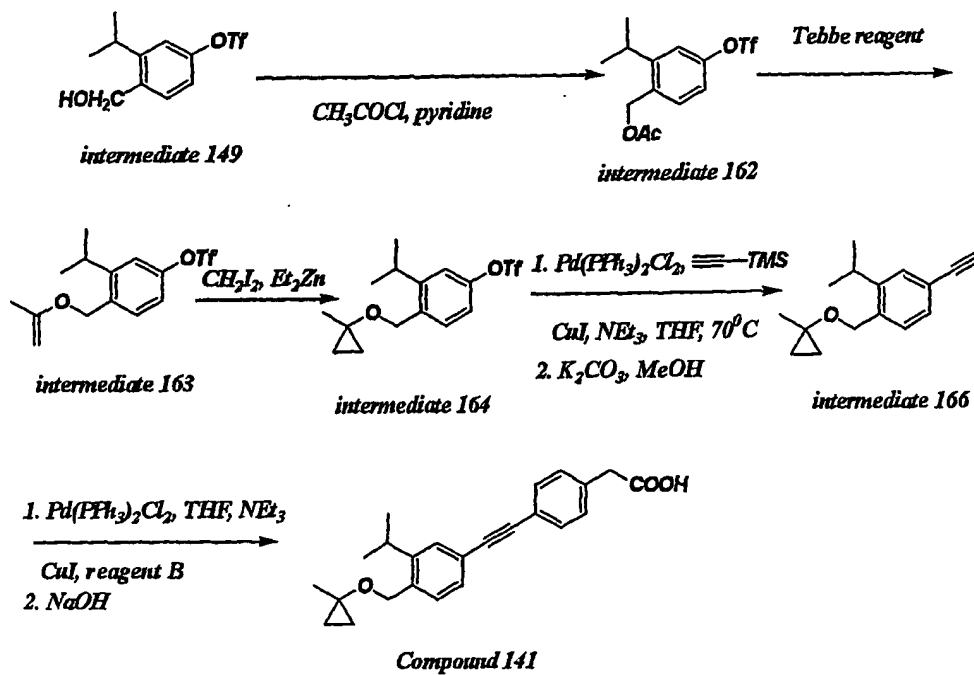
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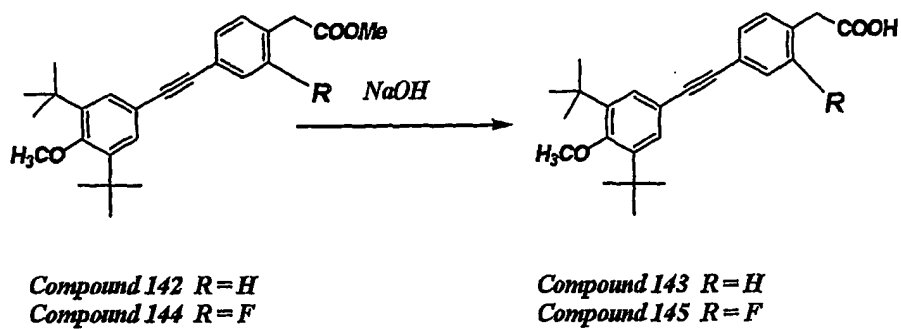
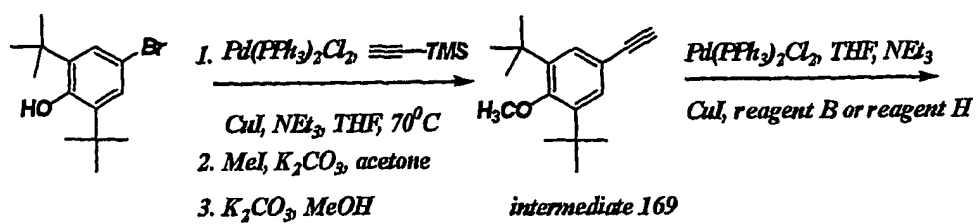
REACTION SCHEME 15



REACTION SCHEME 16

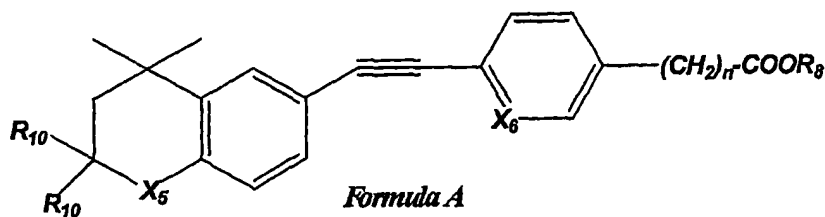


REACTION SCHEME 17



## REACTION SCHEME 18

1 Certain known compounds which have been discovered in accordance  
2 with the present invention to be useful as inhibitors of cytochrome P450RAI  
3 are shown by **Formula A** where  $R_8$  generally represents H, alkyl of 1 to 6  
4 carbons,  $-\text{CH}_2\text{O}(\text{C}_{1-6}\text{-alkyl})$ , or a cation of a pharmaceutically acceptable  
5 base, and where the other variables have the following specific values:



18 In **Compound 201**  $X_5 = \text{O}$ ,  $X_6 = \text{CH}$ ,  $n = 0$ ,  $R_8 = \text{H}$  or a cation of a  
19 pharmaceutically acceptable base and  $R_{10} = \text{CH}_3$ .

20 In **Compound 202**  $X_5 = \text{S}$ ,  $X_6 = \text{CH}$ ,  $n = 1$ ,  $R_8 = \text{H}$  or a cation of a  
21 pharmaceutically acceptable base and  $R_{10} = \text{H}$ .

22 In **Compound 210**  $X_5 = \text{S}$ ,  $X_6 = \text{CH}$ ,  $n = 2$ ,  $R_8 = \text{H}$  or a cation of a  
23 pharmaceutically acceptable base and  $R_{10} = \text{H}$ .

24 In **Compound 215**  $X_5 = \text{S}$ ,  $X_6 = \text{CH}$ ,  $n = 0$ ,  $R_8 = \text{H}$  or a cation of a  
25 pharmaceutically acceptable base and  $R_{10} = \text{H}$ .

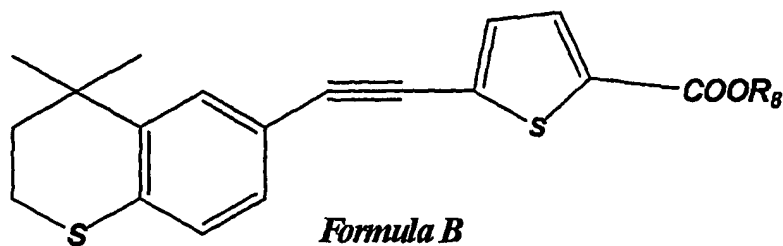
26 In **Compound 238**  $X_5 = \text{S}$ ,  $X_6 = \text{N}$ ,  $n = 0$ ,  $R_8 = \text{H}$  or a cation of a  
27 pharmaceutically acceptable base,  $R_{10} = \text{H}$ .

28 **Compound 201** is described as compound 4 in United States Patent



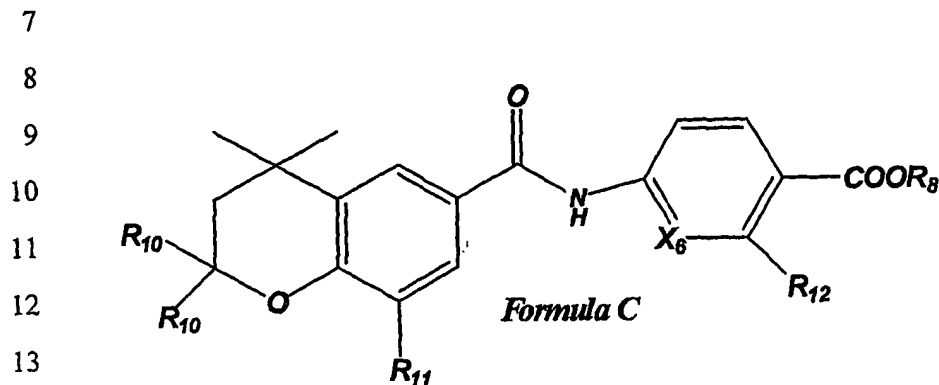
1 No. 4,980,369 incorporated herein by reference. **Compounds 202, 210, and**  
2 **215** are described in United States Patent No. 4,810,804 incorporated herein  
3 by reference. **Compound 215** is example 12 of Patent No. ,4810,804.  
4 **Compound 238** is described in United States Patent No. 5,089,509  
5 incorporated herein by reference (see Claim 5 of Patent No. 5,089,509).

6 Other known compounds which have been discovered in accordance  
7 with the present invention to be useful as inhibitors of cytochrome P450RAI  
8 are shown by **Formula B** where  $R_8$  generally represents H, alkyl of 1 to 6  
9 carbons,  $-\text{CH}_2\text{O}(\text{C}_{1-6}\text{-alkyl})$ , or a cation of a pharmaceutically acceptable  
10 base.



21 Specifically in **Compound 240**  $R_8$  is H or a cation of a pharmaceutically  
22 acceptable base. **Compound 240** is described and can be made in accordance  
23 with the teachings of United States Patent Nos. 5,089,509, ,5,602,130 or  
24 5,348,972 all of which are incorporated herein by reference.

1 Still other known compounds which have been discovered in  
2 accordance with the present invention to be useful as inhibitors of cytochrome  
3 P450RAI are shown by **Formula C** where  $R_8$  generally represents H, alkyl of  
4 1 to 6 carbons,  $-\text{CH}_2\text{O}(\text{C}_{1-6}\text{-alkyl})$ , or a cation of a pharmaceutically  
5 acceptable base, and where the other variables have the following specific  
6 values:

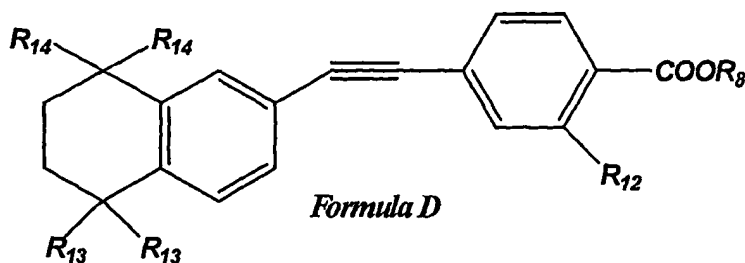


16 In **Compound 203**  $R_8$  is H or a cation of a pharmaceutically acceptable base,  
17  $R_{10} = \text{CH}_3$ ,  $R_{11} = \text{Cl}$ ,  $R_{12} = \text{F}$  and  $X_6 = \text{CH}$ .  
18 In **Compound 204**  $R_8$  is H or a cation of a pharmaceutically acceptable base,  
19  $R_{10} = \text{CH}_3$ ,  $R_{11} = \text{cyclopropyl}$ ,  $R_{12} = \text{F}$  and  $X_6 = \text{CH}$ .  
20 In **Compound 205**  $R_8$  is H or a cation of a pharmaceutically acceptable base,  
21  $R_{10} = \text{CH}_3$ ,  $R_{11} = \text{CF}_3$ ,  $R_{12} = \text{F}$  and  $X_6 = \text{CH}$ .  
22 In **Compound 206**  $R_8$  is H or a cation of a pharmaceutically acceptable base,  
23  $R_{10} = \text{CH}_3\text{CH}_2$ ,  $R_{11} = \text{Br}$ ,  $R_{12} = \text{F}$  and  $X_6 = \text{CH}$ .  
24 In **Compound 220**  $R_8$  is H or a cation of a pharmaceutically acceptable base,  
25  $R_{10} = \text{CH}_3$ ,  $R_{11} = \text{CH}_3$ ,  $R_{12} = \text{F}$  and  $X_6 = \text{CH}$ .  
26 In **Compound 221**  $R_8$  is H or a cation of a pharmaceutically acceptable base,  
27  $R_{10} = \text{CH}_3$ ,  $R_{11} = \text{Cl}$ ,  $R_{12} = \text{F}$  and  $X_6 = \text{N}$ .  
28 In **Compound 224**  $R_8$  is H or a cation of a pharmaceutically acceptable base,

- 1  $R_{10} = CH_3$ ,  $R_{11} = \text{phenyl}$ ,  $R_{12} = F$  and  $X_6 = CH$ .
- 2 In Compound 225  $R_8$  is H or a cation of a pharmaceutically acceptable base,
- 3  $R_{10} = H$ ,  $R_{11} = Br$ ,  $R_{12} = F$  and  $X_6 = CH$ .
- 4 In Compound 226  $R_8$  is H or a cation of a pharmaceutically acceptable base,
- 5  $R_{10} = CH_3$ ,  $R_{11} = OCH_3$ ,  $R_{12} = F$  and  $X_6 = CH$ .
- 6 In Compound 227  $R_8$  is H or a cation of a pharmaceutically acceptable base,
- 7  $R_{10} = CH_3$ ,  $R_{11} = CH_3$ ,  $R_{12} = H$  and  $X_6 = CH$ .
- 8 In Compound 228  $R_8$  is H or a cation of a pharmaceutically acceptable base,
- 9  $R_{10} = CH_3$ ,  $R_{11} = H$ ,  $R_{12} = F$  and  $X_6 = CH$ .
- 10 In Compound 247  $R_8$  is H or a cation of a pharmaceutically acceptable base,
- 11  $R_{10} = CH_3$ ,  $R_{11} = Br$ ,  $R_{12} = F$  and  $X_6 = CH$ .
- 12 In Compound 248  $R_8$  is H or a cation of a pharmaceutically acceptable base,
- 13  $R_{10} = CH_3$ ,  $R_{11} = CF_3CF_2$ ,  $R_{12} = F$  and  $X_6 = CH$ .
- 14 In Compound 249  $R_8$  is H or a cation of a pharmaceutically acceptable base,
- 15  $R_{10} = CH_3$ ,  $R_{11} = CH_3CH_2$ ,  $R_{12} = F$  and  $X_6 = CH$ .
- 16 In Compound 250  $R_8$  is H or a cation of a pharmaceutically acceptable base,
- 17  $R_{10} = CH_3$ ,  $R_{11} = \text{iso-propyl}$ ,  $R_{12} = F$  and  $X_6 = CH$ .
- 18 In Compound 251  $R_8$  is H or a cation of a pharmaceutically acceptable base,
- 19  $R_{10} = CH_3$ ,  $R_{11} = (1\text{-methyl})\text{cyclopropyl}$ ,  $R_{12} = F$  and  $X_6 = CH$ .
- 20 In Compound 252  $R_8$  is H or a cation of a pharmaceutically acceptable base,
- 21  $R_{10} = CH_3$ ,  $R_{11} = \text{tertiary-butyl}$ ,  $R_{12} = F$  and  $X_6 = CH$ .
- 22 In Compound 253  $R_8$  is H or a cation of a pharmaceutically acceptable base,
- 23  $R_{10} = CH_3$ ,  $R_{11} = (2,2\text{-difluoro})\text{cyclopropyl}$ ,  $R_{12} = F$  and  $X_6 = CH$ .
- 24 In Compound 254  $R_8$  is H or a cation of a pharmaceutically acceptable base,
- 25  $R_{10} = CH_3$ ,  $R_{11} = (\text{cyclopropyl})\text{methyl}$ ,  $R_{12} = F$  and  $X_6 = CH$ .
- 26 Compounds 203 - 206, 220, 221, 224 - 228 and 247 - 254 are
- 27 described and can be made in accordance with the teachings of United States
- 28 Patent No. 5,675,024 which is incorporated herein by reference. (Compound

1 205 is compound or example 14, **Compound 225** is compound or example 10,  
2 and **Compound 228** is compound or example 32 in Patent No. 5,675,024.  
3 **Compound 220** is also described in United States Patent No. 5,965,606,  
4 incorporated herein by reference.

5 Still other known compounds which have been discovered in  
6 accordance with the present invention to be useful as inhibitors of cytochrome  
7 P450RAI are shown by **Formula D** where  $R_8$  generally represents H, alkyl of  
8 1 to 6 carbons,  $-CH_2O(C_{1-6}\text{-alkyl})$ , or a cation of a pharmaceutically  
9 acceptable base, and where the other variables have the following specific  
10 values:



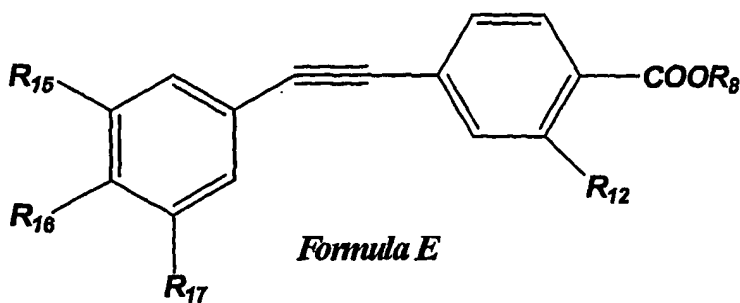
21 In **Compound 207**  $R_8$  is H or a cation of a pharmaceutically acceptable base,  
22  $R_{12} = H$ , the two  $R_{13}$  groups jointly represent an oxo ( $=O$ ) function and  $R_{14} =$   
23  $CH_3$ .

24 In **Compound 208**  $R_8$  is H or a cation of a pharmaceutically acceptable base,  
25  $R_{12} = H$ ,  $R_{13} = H$  and  $R_{14} = CH_3$ .

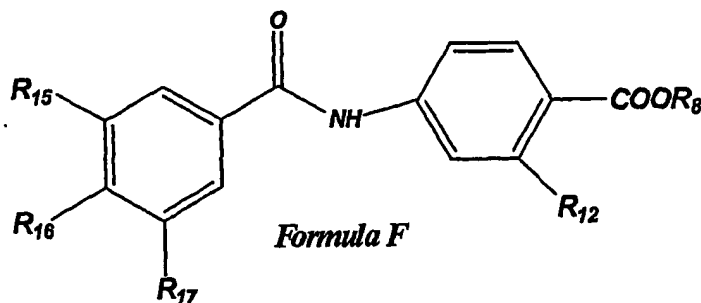
26 In **Compound 216**  $R_8$  is H or a cation of a pharmaceutically acceptable base,  
27  $R_{12} = H$ ,  $R_{13} = CH_3$  and  $R_{14} = CH_3$ .

28 In **Compound 218**  $R_8$  is H or a cation of a pharmaceutically acceptable base,

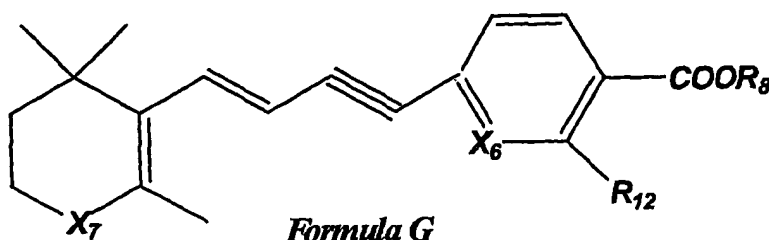
- 1  $R_{12} = H$ ,  $R_{13} = CH_3$  and  $R_{14} = H$ .  
2 In **Compound 230**  $R_8$  is H or a cation of a pharmaceutically acceptable base,  
3  $R_{12} = F$ ,  $R_{13} = CH_3$  and  $R_{14} = CH_3$ .  
4 In **Compound 232**  $R_8$  is H or a cation of a pharmaceutically acceptable base,  
5  $R_{12} = H$ , one of the  $R_{13}$  groups is H, the other is OH and  $R_{14} = CH_3$ .  
6 **Compound 207** is described (as compound 7) in United States Patent  
7 No. 5,489,584 incorporated herein by reference. **Compound 232** is described  
8 (as compound 42) in United States Patent No. 5,654,469 incorporated herein  
9 by reference. **Compounds 208, 216 and 218** are described in the publication  
10 by *Chandraratna et al.* J. Eur. J. Med. Chem., Suppl. to Vol. 30, 1995, 506s-  
11 517s. **Compound 230** can also be made in accordance with the teachings of  
12 the publication by *Chandraratna et al.* J. Eur. J. Med. Chem., Suppl to Vol.  
13 30, 1995, 506s-517s, incorporated herein by reference, or by such modification  
14 of the synthetic procedures of this reference which will be readily apparent to  
15 those skilled in the art.  
16 Still further known compounds which have been discovered in  
17 accordance with the present invention to be useful as inhibitors of cytochrome  
18 P450RAI are shown by **Formula E** where  $R_8$  generally represents H, alkyl of  
19 1 to 6 carbons,  $-CH_2O(C_{1-6}\text{-alkyl})$ , or a cation of a pharmaceutically  
20 acceptable base, and where the other variables have the following specific  
21 values:



- 1 In **Compound 209**  $R_8$  is H or a cation of a pharmaceutically acceptable base,  
2  $R_{12} = H$ ,  $R_{15} = \text{tertiary-butyl}$ ,  $R_{16} = OH$  and  $R_{17} = Cl$ .  
3 In **Compound 211**  $R_8$  is H or a cation of a pharmaceutically acceptable base,  
4  $R_{12} = H$ ,  $R_{15} = \text{tertiary-butyl}$ ,  $R_{16} = OCH_3$  and  $R_{17} = \text{tertiary-butyl}$ .  
5 In **Compound 214**  $R_8$  is H or a cation of a pharmaceutically acceptable base,  
6  $R_{12} = H$ ,  $R_{15} = 1\text{-adamantyl}$ ,  $R_{16} = OCH_3$  and  $R_{17} = H$ .  
7 In **Compound 235**  $R_8$  is H or a cation of a pharmaceutically acceptable base,  
8  $R_{12} = H$ ,  $R_{15} = \text{tertiary-butyl}$ ,  $R_{16} = OH$  and  $R_{17} = \text{tertiary-butyl}$ .  
9 In **Compound 236**  $R_8$  is H or a cation of a pharmaceutically acceptable base,  
10  $R_{12} = F$ ,  $R_{15} = \text{tertiary-butyl}$ ,  $R_{16} = OH$  and  $R_{17} = H$ .  
11 **Compound 211** is described and can be made in accordance with the  
12 teachings of United States Patent No. 5,202,471, and **Compound 235** is  
13 described and can be made in accordance with the teachings of United States  
14 Patent No. 5,498,795. The specification of Patent Nos. 5,202,471 and  
15 5,498,795 are incorporated herein by reference. **Compounds 209, 214** and  
16 **236** can also be made in accordance with the teachings of United States Patent  
17 Nos. 5,202,471 and 5,498,795 with such modifications of the synthetic  
18 procedures which will be readily apparent to those skilled in the art.  
19 Still more known compounds which have been discovered in  
20 accordance with the present invention to be useful as inhibitors of cytochrome  
21 P450RAI are shown by **Formula F** where  $R_8$  generally represents H, alkyl of  
22 1 to 6 carbons,  $-CH_2O(C_{1-6}\text{-alkyl})$ , or a cation of a pharmaceutically  
23 acceptable base, and where the other variables have the following specific  
24 values:



11 In Compound 222  $R_8$  is H or a cation of a pharmaceutically acceptable base,  
12  $R_{12} = F$ ,  $R_{15} = \text{tertiary-butyl}$ ,  $R_{16} = \text{CH}_3\text{CH}_2\text{O}$  and  $R_{17} = \text{I}$ .  
13 In Compound 223  $R_8$  is H or a cation of a pharmaceutically acceptable base,  
14  $R_{12} = F$ ,  $R_{15} = \text{tertiary-butyl}$ ,  $R_{16} = \text{CH}_3\text{CH}_2\text{O}$  and  $R_{17} = \text{Br}$ .  
15 Compounds 222 and 223 are described and can be made in accordance  
16 with the teachings of United States Patent Nos. 5,663,357 and 5,917,048, the  
17 specifications of which are incorporated herein by reference.  
18 Yet more known compounds which have been discovered in  
19 accordance with the present invention to be useful as inhibitors of cytochrome  
20 P450RA1 are shown by Formula G where  $R_8$  generally represents H, alkyl of  
21 1 to 6 carbons,  $-\text{CH}_2\text{O}(\text{C}_{1-6}\text{-alkyl})$ , or a cation of a pharmaceutically  
22 acceptable base, and where the other variables have the following specific  
23 values:



11 In **Compound 212**  $R_8$  is H or a cation of a pharmaceutically acceptable base,

12  $R_{12} = H$ ,  $X_6 = CH$  and  $X_7 = (CH_3)_2C$ .

13 In **Compound 217**  $R_8$  is H or a cation of a pharmaceutically acceptable base,

14  $R_{12} = H$ ,  $X_6 = CH$  and  $X_7 = CH_2$ .

15 In **Compound 219**  $R_8$  is H or a cation of a pharmaceutically acceptable base,

16  $R_{12} = H$ ,  $X_6 = CH$  and  $X_7 = S$ .

17 In **Compound 229**  $R_8$  is H or a cation of a pharmaceutically acceptable base,

18  $R_{12} = F$ ,  $X_6 = CH$  and  $X_7 = CH_2$ .

19 In **Compound 244**  $R_8$  is H or a cation of a pharmaceutically acceptable base,

20  $R_{12} = H$ ,  $X_6 = N$  and  $X_7 = CH_2$ .

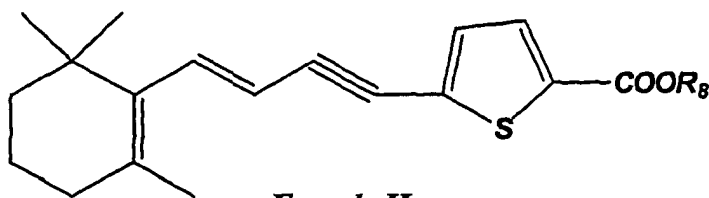
21 **Compounds 217** is described (as example or compound 4) and can be  
22 made in accordance with the teachings of United States Patent Nos. 4,739,098  
23 the specification of which is incorporated herein by reference. **Compounds**

24 **219** is described (as compound 2) and can be made in accordance with the  
25 teachings of United States Patent Nos. 5,688,957, the specification of which is  
26 incorporated herein by reference. **Compound 212** and **Compound 229** can be  
27 made in accordance with the teachings of United States Patent Nos. 4,739,098  
28 and in case of **Compound 212** also in accordance with United States Patent



1 No. 5,426,118, with such modifications of the synthetic procedures which will  
2 be readily apparent to those skilled in the art. The specification of United  
3 States Patent No. 5,426,118 is incorporated herein by reference. **Compound**  
4 **244** is described (as compound or example 7) and can be made in accordance  
5 with the teachings of United States Patent Nos. 4,923,884, the specification of  
6 which is incorporated herein by reference.

7 Still more known compounds which have been discovered in  
8 accordance with the present invention to be useful as inhibitors of cytochrome  
9 P450RAI are shown by **Formula H** where  $R_8$  generally represents H, alkyl of  
10 1 to 6 carbons,  $-\text{CH}_2\text{O}(\text{C}_{1-6}\text{-alkyl})$ , or a cation of a pharmaceutically  
11 acceptable base.



*Formula H*

23 Specifically in **Compound 245**  $R_8$  is H or a cation of a pharmaceutically  
24 acceptable base.

25 **Compounds 245** is described and can be made in accordance with the  
26 teachings of United States Patent Nos. 4,923,884.

1 Further known compounds which have been discovered in accordance  
2 with the present invention to be useful as inhibitors of cytochrome P450RAI  
3 are shown by **Formula I** where  $R_8$  generally represents H, alkyl of 1 to 6  
4 carbons,  $-\text{CH}_2\text{O}(\text{C}_{1-6}\text{-alkyl})$ , or a cation of a pharmaceutically acceptable  
5 base.

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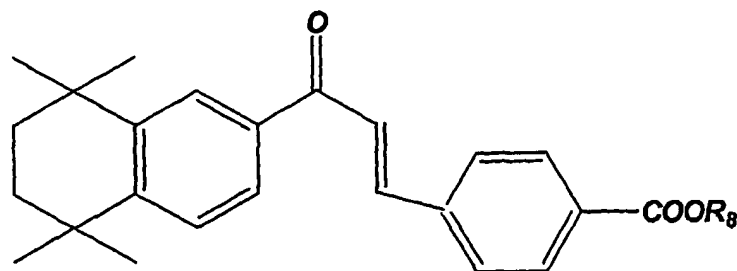
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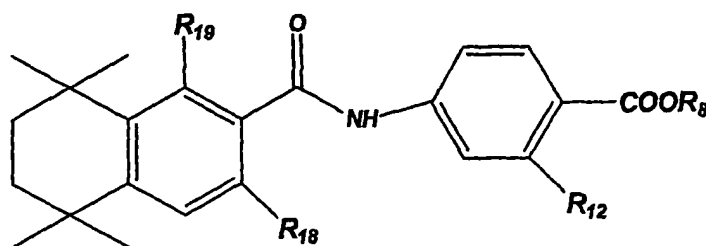


*Formula I*

17 Specifically in **Compound 242**  $R_8$  is H or a cation of a pharmaceutically  
18 acceptable base.

19 **Compound 242** is described in the publication by *Bernard et al.*  
20 *Biochem. Biophys. Res. Commun.*, 1992, Vol. 186, 977-983, incorporated  
21 herein by reference.

1 Still more known compounds which have been discovered in  
2 accordance with the present invention to be useful as inhibitors of cytochrome  
3 P450RAI are shown by **Formula J** where  $R_8$  generally represents H, alkyl of  
4 1 to 6 carbons,  $-\text{CH}_2\text{O}(\text{C}_{1-6}\text{-alkyl})$ , or a cation of a pharmaceutically  
5 acceptable base, and where the other variables have the following specific  
6 values:

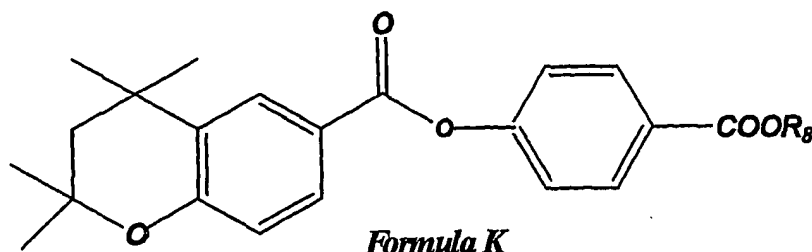


*Formula J*

18 In **Compound 237**  $R_8$  is H or a cation of a pharmaceutically acceptable base,  
19  $R_{12} = \text{F}$ ,  $R_{18} = \text{H}$  and  $R_{19} = \text{H}$ .  
20 In **Compound 246**  $R_8$  is H or a cation of a pharmaceutically acceptable base,  
21  $R_{12} = \text{H}$ ,  $R_{18} = \text{OH}$  and  $R_{19} = \text{F}$ .

22 **Compounds 237 and 246** are described and can be made in accordance  
23 with the teachings of United States Patent Nos. 5,675,024 and 5,856,490.  
24 **Compound 237** is compound or example 2 of Patent No. 5,675,024. The  
25 specification of United States Patent No. 5,856,490 is incorporated herein by  
26 reference.

1 Additional known compounds which have been discovered in  
2 accordance with the present invention to be useful as inhibitors of cytochrome  
3 P450RAI are shown by **Formula K** where  $R_8$  generally represents H, alkyl of  
4 1 to 6 carbons,  $-\text{CH}_2\text{O}(\text{C}_{1-6}\text{-alkyl})$ , or a cation of a pharmaceutically  
5 acceptable base.



17 Specifically in **Compound 231**  $R_8$  is H or a cation of a pharmaceutically  
18 acceptable base.

19 **Compound 231** is described (as compound 2) in United States Patent  
20 No. 5,006,550, the specification of which is incorporated herein by reference.

1 Still more known compounds which have been discovered in  
2 accordance with the present invention to be useful as inhibitors of cytochrome  
3 P450RAI are shown by **Formula L** where  $R_8$  generally represents H, alkyl of  
4 1 to 6 carbons,  $-\text{CH}_2\text{O}(\text{C}_{1-6}\text{-alkyl})$ , or a cation of a pharmaceutically  
5 acceptable base.

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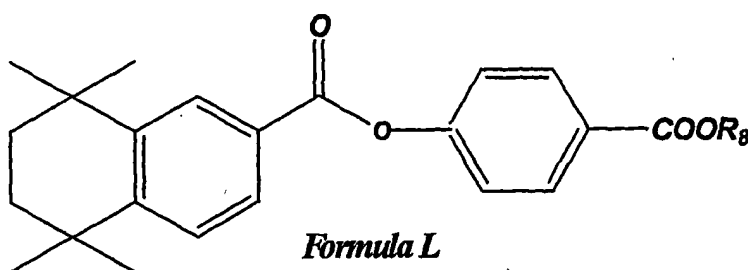
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16 Specifically in **Compound 243**  $R_8$  is H or a cation of a pharmaceutically  
17 acceptable base.

18 **Compound 243** is described (as example or compound 7) in United  
19 States Patent No. 5,130,335, the specification of which is incorporated herein  
20 by reference.

21



1 Still more known compounds which have been discovered in  
2 accordance with the present invention to be useful as inhibitors of cytochrome  
3 P450RAI are shown by **Formula M** where  $R_8$  generally represents H, alkyl of  
4 1 to 6 carbons,  $-\text{CH}_2\text{O}(\text{C}_{1-6}\text{-alkyl})$ , or a cation of a pharmaceutically  
5 acceptable base, and where the other variables have the following specific  
6 values:

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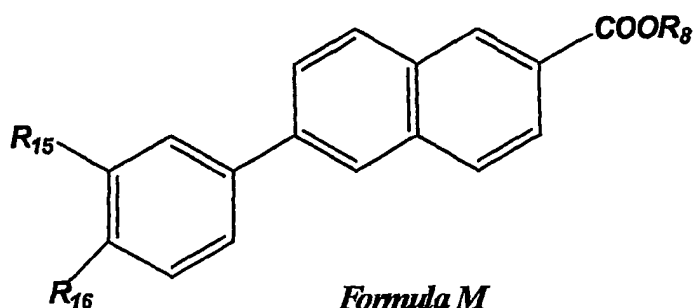
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*Formula M*

16 In **Compound 233**  $R_8$  is H or a cation of a pharmaceutically acceptable base,  
17  $R_{15} = 1\text{-adamantyl}$  and  $R_{16} = \text{OH}$ .

18 In **Compound 234**  $R_8$  is H or a cation of a pharmaceutically acceptable base,  
19  $R_{15} = 1\text{-adamantyl}$  and  $R_{16} = \text{OCH}_3$ .

20 **Compounds 233 and 234** are described in the publication by *Shroot et*  
21 *al.* J. M. EP 199636 (1986) incorporated herein by reference.

1 Further known compounds which have been discovered in accordance  
2 with the present invention to be useful as inhibitors of cytochrome P450RAI  
3 are shown by **Formula N** where  $R_8$  generally represents H, alkyl of 1 to 6  
4 carbons,  $-\text{CH}_2\text{O}(\text{C}_{1-6}\text{-alkyl})$ , or a cation of a pharmaceutically acceptable  
5 base.

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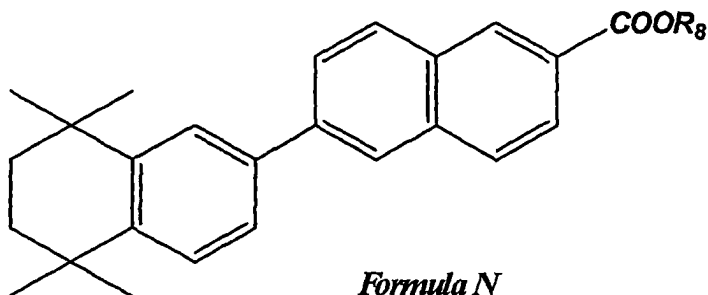
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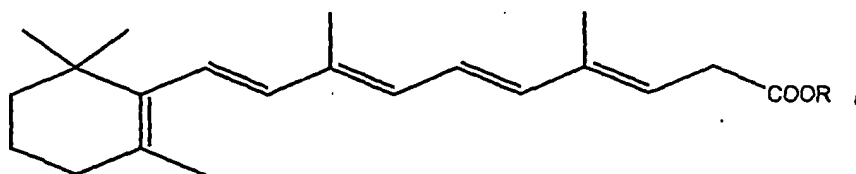
17 Specifically in **Compound 241**  $R_8$  is H or a cation of a pharmaceutically  
18 acceptable base.

19 **Compound 241** is described in the publication by *Dawson et al.* J.  
20 Med. Chem., 1983, Vol. 26, 1653-1656. incorporated herein by reference.



*Formula N*

1 Still further compounds which have been discovered in accordance with  
2 the present invention to be useful as inhibitors of cytochrome P450RAI are  
3 shown by **Formula O** where  $R_8$  generally represents H, alkyl of 1 to 6  
4 carbons,  $-\text{CH}_2\text{O}(\text{C}_{1-6}\text{-alkyl})$ , or a cation of a pharmaceutically acceptable base.



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Formula O

12 Specifically in **Compound 247**  $R_8$  is H or a cation of a  
13 pharmaceutically acceptable base. Compound 247 is described in the  
14 publication by *Winum et al.* Il Farmaco, 1997, Vol. 52, 1, p39-42, incorporated  
15 herein by reference.

16 The P450RAI inhibition data of this compound are provided in **Table**  
17 **1A**, and the cutaneous toxicity score (blackjack score) of the compound in the  
18 topical skin irritation tests provided above, are disclosed in **Table 1B**.



## 1                    SPECIFIC EXAMPLES OF NEW COMPOUNDS

2    4-Hydroxy phenyl acetic acid-*t*-butyl ester (Reagent E)

3                    A stirred suspension of 4-hydroxy-phenyl acetic acid (0.152g, 1mmol)  
4    in anhydrous toluene (5mL) was heated at 80°C and N,N-dimethyl formamide-  
5    di-*t*-butyl acetal (1mL, 4.17mmol) was added when the solution became  
6    homogenous. After 0.5h, the reaction mixture was cooled to ambient  
7    temperature and the volatiles were distilled off in *vacuo*. The residue was  
8    diluted with water and extracted with diethyl ether (x2). The combined  
9    organic extract was dried over anhydrous sodium sulfate, filtered and  
10   evaporated in *vacuo* to afford an oil which was subjected to flash column  
11   chromatography over silica gel (230-400 mesh) using 16% ethyl acetate in  
12   hexane as the eluent to afford the title compound as a solid (0.11g, 56%).  
13   <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 1.44(s, 9H), 3.45(s, 2H), 6.55(s, 1H), 6.69(d, *J*  
14   = 8.8Hz, 2H), 7.06(d, *J* = 8.5Hz, 2H).

15   3-Hydroxy phenyl acetic acid-*t*-butyl ester (Reagent F)

16                    A stirred suspension of 3-hydroxy-phenyl acetic acid (1.52g, 10mmol)  
17   in anhydrous toluene (20mL) was heated at 80°C and N,N-dimethyl  
18   formamide-di-*t*-butyl acetal (9.6mL, 40mmol) was added when the solution  
19   became homogenous. After 0.5h, the reaction mixture was cooled to ambient  
20   temperature and the volatiles were distilled off in *vacuo*. Th residue was  
21   diluted with water and extracted with diethyl ether (x2). The combined  
22   organic extract was dried over anhydrous sodium sulfate, filtered and  
23   evaporated in *vacuo* to afford an oil which was subjected to flash column  
24   chromatography over silica gel (230-400 mesh) using 16% ethyl acetate in  
25   hexane as the eluent to afford the title compound as a solid (1.17g, 56%).  
26   <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 1.47(s, 9H), 3.49(s, 2H), 6.30(s, 1H), 6.70-6.79  
27   (m, 2H), 6.81(d, *J* = 7.6Hz, 1H), 7.16(t, *J* = 7.7Hz, 1H).

28   Methyl-2-fluoro-4-iodo benzoate (Reagent G)

1       A solution of 2-fluoro-4-iodo toluene (5g, 26.6mmol) in pyridine (2mL)  
2 and water (20mL) was treated with potassium permanganate (16.6g,  
3 105mmol) and heated at 150°C overnight. The reaction mixture was then  
4 cooled to room temperature and filtered and the filtrate was extracted with  
5 hexane. The aqueous phase was acidified with 10% hydrochloric acid and  
6 extracted with ethyl acetate. The organic phase was dried over anhydrous  
7 sodium sulfate, filtered and evaporated in *vacuo*. The residue was dissolved  
8 in 20mL of methanol, treated with concentrated sulfuric acid (1mL) and  
9 refluxed overnight. The volatiles were distilled off in *vacuo* and the residue  
10 was dissolved in diethyl ether, washed with brine, dried over anhydrous  
11 sodium sulfate, filtered and evaporated in *vacuo* to an oil. Flash column  
12 chromatography over silica gel (230-400 mesh) using 10% ethyl acetate in  
13 hexane as the eluent afforded the title compound as an oil (0.26g, 5%).

14 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.60 (m, 4H), 3.93 (s, 3H).

15 Ethyl-2-fluoro-4-hydroxy benzoate (Reagent I)

16       A solution of 2-fluoro-4-hydroxy benzoic acid (**Intermediate 4**, 3g,  
17 19.2mmol) in ethanol (65mL) and benzene (90mL) was treated with  
18 concentrated sulfuric acid (1.5mL) and heated at reflux overnight using a  
19 Dean-Stark water trap. The volatiles were distilled off in *vacuo* and the  
20 residue was diluted with water and diethyl ether. The phases were separated  
21 and the organic phase was washed with saturated aqueous sodium bicarbonate  
22 (x1), water (x1) and brine (x1), dried over anhydrous magnesium sulfate,  
23 filtered and evaporated in *vacuo* to afford the title compound as a solid (3.07g,  
24 86%).

25 <sup>1</sup>H-NMR (300 MHz, CD<sub>3</sub>COCD<sub>3</sub>): δ 1.34 (t, *J* = 7.1Hz, 3H), 4.32 (q, *J* =  
26 7.1Hz, 2H), 6.66(dd, *J* = 2.6, 10.9Hz, 1H), 6.76 (dd, *J* = 2.3, 8.5Hz, 1H),  
27 7.83(d, *J* = 8.4Hz, 1H), 9.91 (s, 1H).

28 Ethyl-2-fluoro-4-trifluoromethylsulfonyloxy-benzoate (Intermediate 6)

29       A stirred, cooled (ice bath) solution of ethyl-2-fluoro-4-hydroxy-

1 benzoate (**Intermediate 5**, 0.368g, 2mmol) and 2,6-di-*tert*-butyl-4-methyl-  
2 pyridine (0.81g, 8mmol) in 8mL of dichloromethane was treated with  
3 trifluoromethanesulfonic anhydride (0.1g, 4mmol). The reaction mixture was  
4 allowed to warm to ambient temperature and stirred overnight. The reaction  
5 mixture was subjected to flash column chromatography over silica gel (230-  
6 400 mesh) using 5-10% ethyl acetate in hexane as the eluent to afford the title  
7 compound (0.53g, 85%).

8 <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 1.41 (t, *J* = 7.3Hz, 3H), 4.42 (q, *J* = 7.1Hz,  
9 2H), 7.12-7.20(m, 2H), 8.08(t, *J* = 8.3Hz, 1H).

10 Ethyl-2-fluoro-4-trimethylsilanylethynyl-benzoate (**Intermediate 7**)

11 A solution of ethyl-2-fluoro-4- trifluoromethylsulfonyloxy-benzoate  
12 (**Intermediate 6**, 1.82g, 6mmol) in triethyl amine (12mL) and anhydrous  
13 tetrahydrofuran (30mL) was treated with copper(I)iodide (0.12g, 0.6mmol)  
14 and sparged with argon. Dichlorobis(triphenylphosphine)palladium(II) (0.43g,  
15 0.6mmol) was added followed by (trimethylsilyl)acetylene (3.6mL, 24mmol)  
16 and the resulting reaction mixture was heated at 70°C overnight. It was then  
17 cooled to ambient temperature, diluted with diethyl ether and filtered over a  
18 bed of celite. The filtrate was evaporated in *vacuo* to an oil which was  
19 subjected to flash column chromatography over silica gel (230-400 mesh)  
20 using 5% ethyl acetate in hexane as the eluent to afford the title compound as  
21 an orange oil (1.5g, quantitative).

22 <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>):δ 0.011 (s, 9H), 1.13(t, *J* = 7.1Hz, 3H), 4.13 (q, *J*  
23 = 7.1Hz, 2H), 6.93-7.02(m, 2H), 7.07 (s, 1H), 7.61(t, *J* = 7.9Hz, 1H).

24 Ethyl-4-ethynyl-2-fluoro benzoate (**Reagent D**)

25 A solution of ethyl-2-fluoro-4-trimethylsilanylethynyl-benzoate  
26 (**Intermediate 7**, 1.5g, 6mmol) in ethanol (16mL) was treated with potassium  
27 carbonate (1.485g, 10.74mmol) and stirred overnight at room temperature.  
28 The reaction mixture was then diluted with water and extracted with diethyl  
29 ether (x2). The combined organic phase was dried over anhydrous magnesium

1 sulfate, filtered and evaporated in *vacuo* to afford an orange oil. Flash column  
2 chromatography over silica gel (230-400 mesh) using 5% ethyl acetate in  
3 hexane as the eluent afforded the title compound (1g, 86%).  
4 <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 1.39 (t, *J* = 7.1Hz, 3H), 3.26 (s, 1H), 4.39 (q, *J*  
5 = 7.1Hz, 2H), 7.22-7.33 (m, 2H), 7.88(t, *J* = 7.7Hz, 1H).

6 Methyl-4-iodo-phenyl acetate (Reagent B)

7 A solution of 4-iodo phenyl acetic acid (5g, 19mmol) in methanol was  
8 treated with concentrated sulfuric acid (0.5mL) and refluxed overnight. The  
9 volatiles were distilled off in *vacuo* and the residue was dissolved in ethyl  
10 acetate, washed with brine, dried over anhydrous sodium sulfate, filtered and  
11 evaporated in *vacuo* to an oil which was subjected to flash column  
12 chromatography over silica gel (230-400 mesh) using 5% ethyl acetate in  
13 hexane as the eluent to afford the title compound as a clear oil (5g, 95%).  
14 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.63 (d, 2H, *J* = 8.5Hz), 7.01 (d, 2H, *J* =  
15 8.0Hz), 3.67 (s, 3H), 3.55 (s, 2H).

16 2-Fluoro-4-iodo-phenyl acetonitrile (Intermediate 2)

17 A solution of 2-fluoro-4-iodo-benzyl bromide (**Intermediate 1**, 2.56g,  
18 8.15mmol) in ethanol (55mL and water (10mL) was treated with sodium  
19 cyanide (2.15g, 43.86mmol) and refluxed for 0.5h. The volatiles were distilled  
20 off in *vacuo* and the residue was diluted with water and extracted with diethyl  
21 ether (x2). The combined organic extract was washed with water (x1) and  
22 brine (x1), dried over anhydrous magnesium sulfate, filtered and evaporated in  
23 *vacuo* to afford the title compound as a pale yellow solid (2.05g, 96%).  
24 <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 3.71(s, 3H), 7.16(t, *J* = 8.2Hz, 1H), 7.45(dd, *J*  
25 = 1.7, 9.1Hz, 1H), 7.51(dd, *J* = 1.5, 8.2Hz, 1H).

26 2-Fluoro-4-iodo-phenyl acetic acid (Intermediate 3)

27 A solution of 2-fluoro-4-iodo-phenyl acetonitrile (**Intermediate 2**,  
28 2.05g, 7.83mmol) in ethanol (50mL and water (15mL) was treated with  
29 potassium hydroxide (3.4g, 60.7mmol) and refluxed for 4h. The volatiles were

1 distilled off in *vacuo* and the residue was diluted with water and poured into  
2 cold, dilute hydrochloric acid and the precipitated solid was filtered. The solid  
3 was dissolved in diethyl ether, and the organic solution was dried over  
4 anhydrous magnesium sulfate, filtered and evaporated in *vacuo* to afford the  
5 title compound a pale yellow solid (1.75g, 79%).  
6 <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 3.64 (s, 2H), 6.98(t, *J* = 7.9Hz, 1H), 7.25-7.46  
7 (m, 2H), 9.60-10.40(br s, 1H).

8 Ethyl-2-fluoro-4-iodo-phenyl acetate (Reagent C)

9 A solution of 2-fluoro-iodo-phenyl acetic acid (Intermediate 3, 1.75g,  
10 6.22mmol) in ethanol (50mL) and benzene (100mL) was treated with  
11 concentrated sulfuric acid (1.4mL) and heated at reflux overnight using a  
12 Dean-Stark water trap. The volatiles were distilled off in *vacuo* and the  
13 residue was diluted with water and diethyl ether. The phases were separated  
14 and the organic phase was washed with saturated aqueous sodium bicarbonate  
15 (x1), water (x1) and brine (x1), dried over anhydrous magnesium sulfate,  
16 filtered and evaporated in *vacuo* to afford an oil which was subjected to flash  
17 column chromatography over silica gel (230-400 mesh) using 5%-10% ethyl  
18 acetate in hexane as the eluent to afford the title compound as a pale yellow  
19 solid (1.4g, 73%).

20 <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 1.25 (t, *J* = 7.1Hz, 3H), 3.60 (s, 2H), 4.16 (q, *J*  
21 = 7.1Hz, 2H), 6.99(t, *J* = 8.0Hz, 1H), 7.39-7.44(m, 2H).

22 Methyl-2-fluoro-4-iodo-phenyl acetate (Reagent H)

23 A solution of 2-fluoro-4-iodo-phenyl acetonitrile (Intermediate 2, 3g,  
24 11.45mmol) in methanol (50mL) and benzene (50mL) was treated with *p*-  
25 toluene sulfonic acid (2.5g, 13.15mmol) and heated at reflux overnight using a  
26 Dean-Stark water trap. The volatiles were distilled off in *vacuo* and the  
27 residue was diluted with water and diethyl ether. The phases were separated  
28 and the organic phase was washed with saturated aqueous sodium bicarbonate  
29 (x1), water (x1) and brine (x1), dried over anhydrous magnesium sulfate,

1 filtered and evaporated in *vacuo* to afford an oil which was subjected to flash  
2 column chromatography over silica gel (230-400 mesh) using 6% ethyl acetate  
3 in hexane as the eluent to afford the title compound as a colorless oil (2.7g,  
4 80%).

5 <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 3.62 (s, 2H), 3.70 (s, 3H), 6.99(t, *J* = 7.9Hz,  
6 1H), 7.39-7.45(m, 2H).

7 GENERAL PROCEDURE A: 7-Methoxy-1,1-dimethyl-1,2,3,4-  
8 tetrahydronaphthalene (Intermediate 8)

9 A stirred, cooled (-40°C) solution of titanium tetrachloride in anhydrous  
10 dichloromethane (1M, 20mL) under argon, was treated with a solution of  
11 dimethyl zinc (2M, 40mL) in toluene. After 0.5h, a solution of 7-methoxy-1-  
12 tetralone (1.76g, 10mmol) in anhydrous dichloromethane (5mL) was  
13 cannulated into the reaction mixture and the resulting solution was allowed to  
14 warm to ambient temperature and stirred overnight. The reaction mixture was  
15 then cooled to -40°C and cautiously quenched with methanol (11mL). It was  
16 diluted with dichloromethane and saturated aqueous ammonium chloride  
17 solution. The phases were separated and the aqueous phase was extracted with  
18 dichloromethane (x2mL). The combined organic phase was dried over  
19 anhydrous sodium sulfate, filtered and evaporated in *vacuo* to the title  
20 compound (1.75g, 92%) as an oil.

21 <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>):δ 1.33(s, 6H), 1.67-1.71(m, 2H), 1.79-1.90(m,  
22 2H), 2.75(t, *J* = 6.2Hz, 2H), 3.83(s, 3H), 6.72(dd, *J* = 2.6, 8.3Hz, 1H), 6.93(d,  
23 *J* = 2.6Hz, 1H), 7.02(d, *J* = 8.3Hz, 1H).

24 GENERAL PROCEDURE B: 6-Methoxy-4,4-dimethyl-1,2,3,4-  
25 tetrahydronaphthalene-1-one (Intermediate 9)

26 A solution of 7-methoxy-1,1-dimethyl-1,2,3,4-tetrahydronaphthalene  
27 (Intermediate 8, 1.65g, 8.7 mmol) in 7.5mL of glacial acetic acid was cooled  
28 to 0°C and treated with a solution of chromium trioxide (2g, 20mmol) in 8mL  
29 of acetic acid and 7mL of water. The reaction mixture was then allowed to

1 warm to ambient temperature and stirred overnight. It was diluted with water  
2 and extracted with diethyl ether (x2). The combined organic phase was  
3 washed with water (x1), saturated aqueous sodium bicarbonate (x1) and brine  
4 (x1), dried over anhydrous magnesium sulfate, filtered and evaporated in  
5 *vacuo* to afford the title compound (1.64g, 93%) as a yellow oil.

6 <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 1.34(s, 6H), 1.96(t, *J* = 7.1Hz, 2H), 2.64(t, *J* =  
7 7.1Hz, 2H), 3.83(s, 3H), 6.77(dd, *J* = 2.6, 8.7Hz, 1H), 6.83(d, *J* = 2.5Hz, 1H),  
8 7.98(d, *J* = 8.7Hz, 1H).

9 6-Hydroxy-4,4-dimethyl-1,2,3,4-tetrahydronaphthalene-1-one (**Intermediate**  
10 **10**)

11 A stirred, cooled (-78°C) solution of 6-methoxy-4,4-dimethyl-1,2,3,4-  
12 tetrahydronaphthalene-1-one (**Intermediate 9**, 0.8, 3mmol) under argon was  
13 treated with a 1M solution of boron tribromide (10mL). The reaction mixture  
14 was allowed to warm to ambient temperature and stirred overnight. The  
15 reaction mixture was cooled to -78°C, quenched and diluted with saturated  
16 aqueous sodium bicarbonate solution and the aqueous phase was extracted  
17 with dichloromethane (x2). The combined organic phase was dried over  
18 anhydrous sodium sulfate, filtered and evaporated in *vacuo* to an oil. Flash  
19 column chromatography over silica gel (230-400 mesh) using 30% ethyl  
20 acetate in hexane as the eluent afforded the title compound (0.3g, 52%) as a  
21 yellow viscous oil.

22 <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 1.33(s, 6H), 1.97(t, *J* = 6.8Hz, 2H), 2.71(t, *J* =  
23 6.7Hz, 2H), 6.81(dd, *J* = 2.3, 8.5Hz, 1H), 6.94(d, *J* = 2.3Hz, 1H), 7.98(d, *J* =  
24 8.7Hz, 1H), 9.35(s, 1H).

25 GENERAL PROCEDURE C: 4,4-Dimethyl-6-trifluoromethylsulfonyloxy-  
26 1,2,3,4-tetrahydronaphthalene-1-one (**Intermediate 11**)

27 A stirred, cooled (0°C) solution of 6-hydroxy-4,4-dimethyl-1,2,3,4-  
28 tetrahydronaphthalene-1-one (**Intermediate 10**, 0.3g, 1.6mmol) in anhydrous  
29 dichloromethane (10mL) was treated with 4-(dimethylamino)pyridine (0.36g,

1 3.27mmol) followed by 2-[N,N'-bis(trifluoromethylsulfonyl)amino]-5-  
2 chloropyridine (0.79g, 2mmol). After stirring at ambient temperature for  
3 0.75h, the reaction mixture was diluted with dichloromethane and washed with  
4 water (x1). The organic phase was dried over anhydrous sodium sulfate,  
5 filtered and evaporated in *vacuo* to an oil. Flash column chromatography over  
6 silica gel (230-400 mesh) using 8-10% ethyl acetate in hexane as the eluent  
7 afforded the title compound (0.462g, 90%) as an off-white solid.  
8 <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 1.36(s, 6H), 2.01(t, *J* = 6.8Hz, 2H), 2.70(t, *J* =  
9 6.7Hz, 2H), 7.15(dd, *J* = 2.5, 8.7Hz, 1H), 7.28(d, *J* = 2.4Hz, 1H), 8.06(d, *J* =  
10 8.7Hz, 1H).

11 GENERAL PROCEDURE D: 4,4-Dimethyl-6-trimethylsilanyl-ethynyl-  
12 1,2,3,4-tetrahydronaphthalene-1-one (Intermediate 12)

13 A solution of 4,4-dimethyl-6-trifluoromethylsulfonyloxy-1,2,3,4-  
14 tetrahydronaphthalene-1-one (Intermediate 11, 0.46g, 1.43mmol) in triethyl  
15 amine (3mL) and anhydrous tetrahydrofuran (8mL) was treated with  
16 copper(I)iodide (0.1g, 0.53mmol) and sparged with argon for 5 minutes.  
17 Trimethylsilyl acetylene (0.85mL, 6mmol) was then added followed by  
18 dichlorobis(triphenylphosphine)palladium(II) (0.25g, 0.36mmol). The  
19 resulting reaction mixture was heated at 70°C for 17h. It was then cooled to  
20 ambient temperature, diluted with diethyl ether and filtered over a bed of  
21 celite. The filtrate was evaporated *vacuo* to an oil which was subjected to  
22 flash column chromatography over silica gel (230-400 mesh) using 5% ethyl  
23 acetate in hexane as the eluent to afford the title compound (0.28g, 72%).  
24 <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 0.26(s, 9H), 1.36(s, 6H), 1.99(t, *J* = 6.8Hz,  
25 2H), 2.69(t, *J* = 6.7Hz, 2H), 7.35(dd, *J* = 1.7, 8.2Hz, 1H), 7.49 (unresolved d,  
26 1H), 7.93(d, *J* = 8.1Hz, 1H).

27 GENERAL PROCEDURE E: 6-Ethynyl-4,4-dimethyl-1,2,3,4-  
28 tetrahydronaphthalene-1-one (Intermediate 13)



1 A solution of 4,4-dimethyl-6-trimethylsilanylethynyl-1,2,3,4-  
2 tetrahydronaphthalene-1-one (**Intermediate 12**, 0.28g, 1.03mmol) in methanol  
3 (10mL) was treated with potassium carbonate (0.74g, 5.35mmol) and stirred at  
4 ambient temperature for 4h. The volatiles were distilled off in *vacuo* and the  
5 residue was diluted with water and extracted with diethyl ether (x2). The  
6 combined organic extract was dried over anhydrous magnesium sulfate,  
7 filtered and evaporated in *vacuo* to afford the title compound (0.19g, 89%) as  
8 an oil that solidified on standing.  
9 <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 1.33(s, 6H), 1.96(t, *J* = 6.8Hz, 2H), 2.67(t, *J* =  
10 6.8Hz, 2H), 3.25(s, 1H), 7.33(dd, *J* = 1.5, 8.1Hz, 1H), 7.49 (d, *J* = 1.5Hz,  
11 1H), 7.13(d, *J* = 8.1Hz, 1H).

12 GENERAL PROCEDURE F: 4-(8,8-Dimethyl-5-oxo-5,6,7,8-tetrahydro-  
13 naphthalene-2-yl-ethynyl)-benzoic acid ethyl ester (**Intermediate 14**)

14 A solution of 6-ethynyl-4,4-dimethyl-1,2,3,4-tetrahydronaphthalene-1-  
15 one (**Intermediate 13**, 0.23g, 1.1mmol) and ethyl-4-iodo benzoate (**Reagent**  
16 **A**, 0.36g, 1.3mmol) in triethyl amine (7mL) and anhydrous tetrahydrofuran  
17 (3mL) was treated with copper(I)iodide (0.114g, 0.6mmol) and sparged with  
18 argon for 5 minutes. Dichlorobis(triphenylphosphine)palladium(II) (0.23g,  
19 0.33mmol) was added and the reaction mixture was stirred overnight at room  
20 temperature. It was diluted with diethyl ether and filtered over a bed of celite.  
21 The filtrate was evaporated in *vacuo* to a brown oil that was subjected to flash  
22 column chromatography over silica gel (230-400 mesh) using 6-7% ethyl  
23 acetate in hexane as the eluent to afford the title compound (0.29g, 72%) as a  
24 pale brown solid.  
25 <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 1.3(t, *J* = 7.1Hz, 3H), 1.37(s, 6H), 1.80 (t, *J* =  
26 6.8Hz, 2H), 2.69(t, *J* = 6.8Hz, 2H), 4.35(q, *J* = 7.1Hz, 2H), 7.40(dd, *J* = 1.5,  
27 8.2Hz, 1H), 7.51 (d, *J* = 1.6Hz, 1H), 7.57 (d, *J* = 8.3Hz, 2H), 7.96(d, *J* =  
28 8.2Hz, 1H), 7.99(d, *J* = 8.5Hz, 2H).

1 GENERAL PROCEDURE G 4-(5-Cyclopropylamino-8,8-dimethyl-5,6,7,8-  
2 tetrahydro-naphthalene-2-yl-ethynyl)-benzoic acid ethyl ester (Compound 1,  
3 **General Formula 4)**

4 A solution of 4-(8,8-dimethyl-5-oxo-5,6,7,8-tetrahydro-naphthalene-2-  
5 ylethynyl)-benzoic acid ethyl ester (**Intermediate 14**, 0.14g, 0.4mmol) in 3mL  
6 of dichloromethane and 2mL of acetonitrile was treated with cyclopropyl  
7 amine(1mL, 14.45mmol). After 5 minutes, acetic acid (1mL) was added  
8 followed by sodium cyanoborohydride (0.13g, 2mmol). The reaction was  
9 stirred overnight at ambient temperature. It was then diluted with water and  
10 saturated aqueous sodium carbonate solution and extracted with  
11 dichloromethane (x2). The combined organic extract was dried over  
12 anhydrous sodium sulfate, filtered and evaporated in *vacuo* to an oil. Flash  
13 column chromatography over silica gel (230-400 mesh) using 20% ethyl  
14 acetate in hexane as the eluent afforded the title compound (0.1g, 62%) as a  
15 pale yellow solid.

16 <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 0.30-0.60(m, 4H), 1.28(s, 3H), 1.35 (s, 3H),  
17 1.30(t, *J* = 7.1Hz, 3H), 1.55-1.61(m, 1H), 1.83-2.05(m, 3H), 2.25 (quintet, *J* =  
18 3.0 Hz, 1H), 3.80 (t, *J* = 4.9Hz, 1H), 4.39(q, *J* = 7.1Hz, 2H), 7.27-7.36(m,  
19 2H), 7.52 (s, 1H), 7.55(d, *J* = 8.3Hz, 2H), 8.03(d, *J* = 8.5Hz, 2H).

20 GENERAL PROCEDURE H 4-[(5-Cyclopropyl-methyl-amino)-8,8-dimethyl-  
21 5,6,7,8-tetrahydro-naphthalene-2-ylethynyl]-benzoic acid ethyl ester  
22 **(Compound 2, General Formula 4)**

23 A solution of 4-(5-cyclopropylamino-8,8-dimethyl-5,6,7,8-tetrahydro-  
24 naphthalene-2-ylethynyl)-benzoic acid ethyl ester (**Compound 1**, 0.064g,  
25 0.16mmol) in acetone (2mL) was treated with potassium carbonate (0.6g,  
26 4.34mmol) and methyl iodide (1mL, 16mmol) and stirred overnight at ambient  
27 temperature. The volatiles were distilled off in *vacuo* and the residue was  
28 diluted with water and extracted with dichloromethane (x2). The combined

1 organic extract was dried over anhydrous sodium sulfate, filtered and  
2 evaporated in *vacuo* to afford the title compound (0.065g, 99%).  
3 <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 0.28-0.49 (m, 4H), 1.21(s, 3H), 1.26 (s, 3H),  
4 1.33 (t, *J* = 7.1Hz, 3H), 1.58-1.73 (m, 2H), 1.83-1.89 (m, 2H), 2.02-2.08 (m,  
5 1H), 2.06 (s, 3H), 3.88 (t, *J* = 8.1Hz, 1H), 4.32(q, *J* = 7.1Hz, 2H), 7.20(d, *J* =  
6 7.8Hz, 1H), 7.41 (s, 1H), 7.46 (d, *J* = 7.8Hz, 1H), 7.52(d, *J* = 8.4Hz, 2H),  
7 8.03(d, *J* = 8.3Hz, 2H).

8 GENERAL PROCEDURE I: 4-[(5-Cyclopropyl-methyl-amino)-8,8-dimethyl-  
9 5,6,7,8-tetrahydro-naphthalene-2yl-ethynyl]-benzoic acid (Compound 3,  
10 **General Formula 4**) A solution of 4-[(5-cyclopropyl-methyl-amino)-8,8-  
11 dimethyl-5,6,7,8-tetrahydro-naphthalene-2-ylethynyl]-benzoic acid ethyl ester  
12 (Compound 2, 0.065g, 0.158mmol) in ethanol (1mL) and tetrahydrofuran  
13 (1mL) was treated with 1M aqueous sodium hydroxide solution (1mL) and  
14 heated at 80°C for 1h. The volatiles were distilled off in *vacuo* and the residue  
15 was diluted with saturated aqueous ammonium chloride solution and extracted  
16 with ethyl acetate (x2). The combined organic extract was dried over  
17 anhydrous sodium sulfate, filtered and evaporated in *vacuo* to afford a solid  
18 that was washed with dichloromethane and dried to afford the title compound  
19 (0.029g, 38%) as a white solid.

20 <sup>1</sup>H-NMR (300 MHz, CD<sub>3</sub>COCD<sub>3</sub>): δ 0.35-0.51(m, 4H), 1.26(s, 3H), 1.29 (s,  
21 3H), 1.60-1.82(m, 2H), 1.88-2.02(m, 2H), 2.02-2.15 (m, 1H), 2.10 (s, 3H),  
22 3.93 (t, *J* = 8.0Hz, 1H), 7.26(dd, *J* = 1.5, 8.2Hz, 1H), 7.51 (d, *J* = 1.5Hz, 1H),  
23 7.52(d, *J* = 8.2Hz, 1H), 7.62(d, *J* = 8.5Hz, 2H), 8.02(d, *J* = 8.2Hz, 2H).  
24 4-[(8,8-Dimethyl-5-oxo-5,6,7,8-tetrahydro-naphthalene-2-yl-ethynyl)-phenyl]-  
25 acetic acid methyl ester (Compound 4, General Formula 8)

26 Following general procedure F and using 6-ethynyl-4,4-dimethyl-  
27 1,2,3,4-tetrahydronaphthalene-1-one (Intermediate 13, 0.312g, 1.5mmol), 4-  
28 iodo phenyl acetic acid methyl ester (Reagent B, 0.50g, 1.8mmol), triethyl  
29 amine (7mL), anhydrous tetrahydrofuran (3mL), copper(I)iodide (0.04g,

1 0.2mmol) and dichlorobis(triphenylphosphine)palladium(II) (0.15g,  
2 0.213mmol) followed by flash column chromatography over silica gel (230-  
3 400 mesh) using 16-20% ethyl acetate in hexane as the eluent, the title  
4 compound was obtained as a pale yellow solid (0.42g, 76%).  
5 <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 1.42(s, 6H), 2.04(t, *J* = 6.7Hz, 2H), 2.74(t, *J* =  
6 6.7Hz, 2H), 3.66(s, 2H), 3.71(s, 3H), 7.29 (d, *J* = 8.2Hz, 2H), 7.43(dd, *J* = 1.5,  
7 7.9Hz, 1H), 7.52 (d, *J* = 8.2Hz, 2H), 7.57 (d, *J* = 1.5Hz, 1H), 8.00(d, *J* =  
8 8.2Hz, 1H).

9 GENERAL PROCEDURE J: 4-[(8,8-Dimethyl-5-oxo-5,6,7,8-tetrahydro-  
10 naphthalene-2-yl-ethynyl)-phenyl]-acetic acid (Compound 5, General  
11 Formula 8)

12 A solution of 4-[(8,8-dimethyl-5-oxo-5,6,7,8-tetrahydro-naphthalene-  
13 2-ylethynyl)-phenyl]-acetic acid methyl ester (Compound 4, 0.1g, 0.28mmol)  
14 in a mixture of methanol (2mL), tetrahydrofuran (3.5mL) and water (1.5mL)  
15 was treated with lithium hydroxide monohydrate (0.11g, 2.62mmol) and the  
16 resulting reaction mixture was stirred at ambient temperature for 3h. The  
17 volatiles were distilled off in *vacuo* and the residue was diluted with water and  
18 dilute hydrochloric acid and extracted with ethyl acetate (x3). The combined  
19 organic phase was dried over anhydrous sodium sulfate, filtered and  
20 evaporated in *vacuo* to afford the title compound as a pale yellow solid  
21 (0.088g, 92%).

22 <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 1.41(s, 6H), 2.02(t, *J* = 6.7Hz, 2H), 2.74(t, *J* =  
23 6.8Hz, 2H), 3.68(s, 2H), 7.28 (d, *J* = 8.2Hz, 2H), 7.42(dd, *J* = 1.5, 8.2Hz, 1H),  
24 7.52 (d, *J* = 8.2Hz, 2H), 7.56 (d, *J* = 1.5Hz, 1H), 7.99(d, *J* = 8.2Hz, 1H).  
25 4-[(5-(Cyclopropyl-amino)-8,8-dimethyl- 5,6,7,8-tetrahydro-naphthalene-2-yl-  
26 ethynyl)-phenyl]-acetic acid methyl ester (Compound 6, General Formula  
27 4)

28 Following general procedure G and using 4-[(8,8-dimethyl-5-oxo-  
29 5,6,7,8-tetrahydro-naphthalene-2-yl-ethynyl)-phenyl]-acetic acid methyl ester

1 (Compound 4, 0.2g, 0.54mmol), dichloromethane (4mL), acetonitrile(2mL),  
2 cyclopropyl amine(1mL, 14.45mmol), acetic acid (1mL)and sodium  
3 cyanoborohydride (0.16g, 2.54mmol) followed by flash column  
4 chromatography over silica gel (230-400 mesh) using 30% ethyl acetate in  
5 hexane as the eluent the title compound was obtained as a pale yellow oil  
6 (0.22g, 99%).

7 <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 0.38-0.60 (m, 4H), 1.26(s, 3H), 1.33(s, 3H),  
8 1.50-1.59(m, 1H), 1.79-2.10 (m, 3H), 2.25(m, 1H), 3.63(s, 2H), 3.69(s, 3H),  
9 3.79(t, *J* = 4.8Hz, 1H), 7.20-7.32 (m, 4H), 7.47(s, 1H), 7.58(d, *J* = 8.2Hz, 2H).

10 4-[(5-(Cyclopropyl-methyl-amino)-8,8-dimethyl- 5,6,7,8-tetrahydro-  
11 naphthalene-2-yl-ethynyl)-phenyl]-acetic acid methyl ester (Compound 7,  
12 **General Formula 4)**

13 Following general procedure H and using 4-[(5-(cyclopropyl-amino)-  
14 8,8-dimethyl- 5,6,7,8-tetrahydro-naphthalene-2-ylethynyl)-phenyl]-acetic acid  
15 methyl ester (Compound 6, 0.15g, 0.37mmol), acetone (5mL), potassium  
16 carbonate (1.1g, 7.95mmol) and methyl iodide (1mL, 16mmol), the following  
17 work-up was used. The volatiles were distilled off in *vacuo* and the residue  
18 was diluted with water and extracted with dichloromethane (x2). The  
19 combined organic extract was dried over anhydrous sodium sulfate, filtered  
20 and evaporated in *vacuo* to afford the title compound (0.148g, 97%).

21 <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 0.38-0.58(m, 4H), 1.27(s, 3H), 1.31 (s, 3H),  
22 1.68-1.81(m, 2H), 1.85-1.98(m, 2H), 2.08-2.15 (m, 1H), 2.12 (s, 3H), 3.62(s,  
23 2H), 3.69(s, 3H), 3.94 (t, *J* = 7.9Hz, 1H), 7.24(d, *J* = 8.2Hz, 1H), 7.24 (d, *J* =  
24 8.2Hz, 2H), 7.44-7.51(m, 4H).

25 4-[(5-(Cyclopropyl-methyl-amino)-8,8-dimethyl- 5,6,7,8-tetrahydro-  
26 naphthalene-2-yl-ethynyl)-phenyl]-acetic acid (Compound 8, General  
27 **Formula 4)**

28 Following general procedure J and using 4-[(5-(cyclopropyl-methyl-  
29 amino)-8,8-dimethyl-5,6,7,8-tetrahydro-naphthalene-2ylethynyl)-phenyl]-

1 acetic acid methyl ester (**Compound 7**, 0.148g, 0.357mmol), methanol (2mL),  
2 tetrahydrofuran (4mL), water (1mL) and lithium hydroxide monohydrate  
3 (0.25g, 5.95mmol) followed by flash column chromatography over silica gel  
4 (230-400 mesh) using 30-75% ethyl acetate in hexane as the eluent, the title  
5 compound was obtained as a white solid (0.08g, 56%).  
6 <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 0.52-0.54(m, 2H), 0.68-0.70(m, 2H), 1.27(s,  
7 3H), 1.29(s, 3H), 1.63-1.80(m, 2H), 1.95-2.17(m, 2H), 2.19-2.24(m, 1H),  
8 2.24(s, 3H), 3.60(s, 2H), 4.18(t, *J* = 7.7Hz, 1H), 7.24(dd, *J* = 1.5, 8.2Hz, 1H),  
9 7.26 (d, *J* = 8.2Hz, 2H), 7.43 (d, *J* = 8.2Hz, 1H), 7.47(s, 1H), 7.47(d, *J* =  
10 8.2Hz, 2H), 10.37(br s, 1H).

11 2-Fluoro-4-[(8,8-dimethyl-5-oxo-5,6,7,8-tetrahydro-naphthalen-2-yl-  
12 ethynyl)]benzoic acid ethyl ester (**Compound 9**, General Formula 8)

13 A solution of 4,4-dimethyl-6-trifluoromethylsulfonyloxy-1,2,3,4-  
14 tetrahydronaphthalene-1-one (**Intermediate 11**, 0.3g, 0.9mmol),  
15 copper(I)iodide (0.057g, 0.3mmol) and ethyl-2-fluoro-4-ethynyl-benzoate  
16 (**Reagent D**, 0.44g, 2.27mmol) in triethyl amine (2mL) and tetrahydrofuran  
17 (3mL) was sparged with argon for 5 minutes and treated with  
18 dichlorobis(triphenylphosphine)palladium(II) (0.135g, 0.192mmol) and stirred  
19 at room temperature overnight and then refluxed for 2h. It was then cooled to  
20 ambient temperature, diluted with diethyl ether and filtered over a bed of  
21 celite. The filtrate was evaporated in *vacuo* to an oil which was subjected to  
22 flash column chromatography over silica gel (230-400 mesh) using 10-15%  
23 ethyl acetate in hexane as the eluent to afford the title compound as a yellow  
24 solid (0.22g, 67%).

25 <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 1.38 (t, *J* = 7.0Hz, 3H), 1.39(s, 6H), 2.01(t, *J*  
26 = 6.7Hz, 2H), 2.71(t, *J* = 6.7Hz, 2H), 4.37(q, *J* = 7Hz, 2H), 7.28(dd, *J* = 0.9,  
27 10Hz, 1H), 7.34(dd, *J* = 0.9, 8.2Hz, 1H), 7.41 (dd, *J* = 1.5, 8.2Hz, 1H), 7.57(d,  
28 *J* = 0.9Hz), 7.90(t, *J* = 7.9Hz, 1H), 7.93 (d, *J* = 7.9Hz, 1H).

1 2-Fluoro-4-(8,8-dimethyl-5-oxo-5,6,7,8-tetrahydro-naphthalen-2-yl-ethynyl)-  
2 benzoic acid (Compound 10, General Formula 8)

3 A solution of 2-fluoro-4-(8,8-dimethyl-5-oxo-5,6,7,8-tetrahydro-  
4 naphthalen-2-ylethynyl)benzoic acid ethyl ester (**Compound 9**, 0.1g,  
5 0.274mmol) in ethanol(4mL), methanol (2mL) and tetrahydrofuran (2mL) was  
6 treated with 1M aqueous sodium hydroxide solution and heated at 70°C for  
7 1h. The volatiles were distilled off in *vacuo* and the residue was diluted with  
8 water and dilute hydrochloric acid and extracted with ethyl acetate (x2). The  
9 combined organic extract was dried over anhydrous sodium sulfate, filtered  
10 and evaporated in *vacuo* to afford a solid that was recrystallized from hot  
11 aqueous acetonitrile to afford the title compound (0.025g, 27%).

12 <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 1.43(s, 6H), 2.05(t, *J* = 6.9Hz, 2H), 2.76(t, *J* =  
13 6.9Hz, 2H), 7.26-7.47(m, 3H), 7.60(d, *J* = 1.1Hz, 1H), 7.99-8.05(m, 2H).

14 4-[5-(Cyclopropyl-amino)-8,8-dimethyl-5,6,7,8-tetrahydro-naphthalene-2-yl-  
15 ethynyl]-2-fluoro-benzoic acid ethyl ester (Compound 11, General Formula  
16 4)

17 Following general procedure G and using 2-fluoro-4-(8,8-dimethyl-5-  
18 oxo-5,6,7,8-tetrahydro-naphthalene-2-ylethynyl)-benzoic acid ethyl ester  
19 (**Compound 9**, 0.132g, 0.3mmol), dichloromethane (4mL), acetonitrile(2mL),  
20 cyclopropyl amine(1mL, 14.45mmol), acetic acid (1mL)and sodium  
21 cyanoborohydride (0.18g, 2.86mmol) followed by flash column  
22 chromatography over silica gel (230-400 mesh) using 16-20% ethyl acetate in  
23 hexane as the eluent, the title compound was obtained as a pale yellow oil  
24 (0.1g, 82%).

25 <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>):δ 0.36-0.54 (m, 4H), 1.27(s, 3H), 1.33(s, 3H),  
26 1.40(t, *J* = 7.0Hz, 3H), 1.54-1.61(m, 2H), 1.82-2.05 (m, 2H), 2.26(m, 1H),  
27 3.79 (t, *J* = 4.9Hz, 1H), 4.39(q, *J* = 7.1Hz, 2H), 7.26-7.50(m, 4H), 7.87(s, 1H),  
28 7.92 (t, *J* = 7.9Hz, 1H).

1 4-[5-(Cyclopropyl-methyl-amino)-8,8-dimethyl- 5,6,7,8-tetrahydro-  
2 naphthalene-2-yl-ethynyl]-2-fluoro benzoic acid ethyl ester (Compound 12,  
3 **General Formula 4)**

4       Following general procedure H and using 4-[5-(cyclopropyl-methyl-  
5 amino)-8,8-dimethyl- 5,6,7,8-tetrahydro-naphthalene-2-ylethynyl]-2-fluoro-  
6 benzoic acid ethyl ester (**Compound 11**, 0.1g, 0.246mmol), acetone (4mL),  
7 potassium carbonate (0.917g, 6.63mmol) and methyl iodide (0.8mL, 11mmol),  
8 the following work-up was used. The volatiles were distilled off in *vacuo* and  
9 the residue was diluted with water and extracted with dichloromethane (x2).  
10 The combined organic extract was dried over anhydrous sodium sulfate,  
11 filtered and evaporated in *vacuo* to an oil. Flash column chromatography over  
12 silica gel (230-400 mesh) using 8-10% ethyl acetate in hexane as the eluent  
13 afforded the title compound as a pale yellow oil (0.102g, 98%).  
14 <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 0.39-0.62 (m, 4H), 1.29(s, 3H), 1.34(s, 3H),  
15 1.42(t, *J* = 6.9Hz, 3H), 1.65-1.82(m, 2H), 1.85-2.02 (m, 2H), 2.02-2.10(m,  
16 1H), 2.15(s, 3H), 3.97(t, *J* = 7.7Hz, 1H), 4.42(q, *J* = 7.0Hz, 2H), 7.28-7.36 (m,  
17 3H), 7.59(s, 1H), 7.55(d, *J* = 7.9Hz, 2H), 7.92 (t, *J* = 7.5Hz, 1H).  
18 4-[5-(Cyclopropyl-methyl-amino)-8,8-dimethyl- 5,6,7,8-tetrahydro-  
19 naphthalene-2-yl-ethynyl]-2-fluoro benzoic acid (Compound 13, General  
20 **Formula 4)**

21       Following general procedure I and using 4-[(5-cyclopropyl-methyl-  
22 amino)-8,8-dimethyl-5,6,7,8-tetrahydro-naphthalene-2-ylethynyl]-2-fluoro-  
23 benzoic acid ethyl ester (**Compound 12**, 0.102g, 0.23mmol), ethanol (4mL)  
24 and 1M aqueous sodium hydroxide solution (2mL) followed by flash column  
25 chromatography over silica gel (230-400 mesh) 30% ethyl acetate in hexane as  
26 the eluent, the title compound was obtained as an off-white solid(0.015g,  
27 16%).  
28 <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 0.54-0.65 (m, 4H), 1.29 (s, 3H), 1.32 (s, 3H),  
29 1.68-1.83 (m, 2H), 1.97-2.05 (m, 2H), 2.18-2.25 (m, 1H), 2.25 (s, 3H), 4.13 (t,



1  $J = 6.7\text{Hz}$ , 1H), 7.26-7.30 (m, 2H), 7.34 (dd,  $J = 1.5$ , 7.9Hz, 1H), 7.48 (d,  $J =$   
2 1.8Hz, 1H), 7.60 (d,  $J = 8.5\text{Hz}$ , 1H), 7.95 (t,  $J = 7.9\text{Hz}$ , 1H).

3 [2-Fluoro-4-(8,8-dimethyl-5-oxo-5,6,7,8-tetrahydro-naphthalene-2-yl)-  
4 ethynyl]-phenyl]acetic acid ethyl ester (**Compound 14**, General Formula 8)

5 Following general procedure F and using 6-ethynyl-4,4-dimethyl-  
6 1,2,3,4-tetrahydro-naphthalene-1-one (**Intermediate 13**, 0.298g, 1.43mmol),  
7 2-fluoro-4-iodo phenyl acetic acid ethyl ester (**Reagent C**, 0.44g, 1.43mmol),  
8 triethyl amine (**Intermediate 13**, 3mL), anhydrous tetrahydrofuran (7mL),  
9 copper(I)iodide (0.04g, 0.2mmol) and  
10 dichlorobis(triphenylphosphine)palladium(II) (0.15g, 0.213mmol) followed by  
11 flash column chromatography over silica gel (230-400 mesh) using 14-16%  
12 ethyl acetate in hexane as the eluent, the title compound was obtained as an oil  
13 (0.43g, 77%).

14  $^1\text{H-NMR}$  (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.26(t,  $J = 7.2\text{Hz}$ , 3H), 1.41(s, 6H), 2.04(t,  $J =$   
15 6.7Hz, 2H), 2.74(t,  $J = 6.7\text{Hz}$ , 2H), 3.68(s, 2H), 4.18(q,  $J = 7.1\text{Hz}$ , 2H), 7.23-  
16 7.57(m, 4H), 7.59 (d,  $J = 1.5\text{Hz}$ , 1H), 7.99(d,  $J = 7.9\text{Hz}$ , 1H).

17 [2-Fluoro-4-(8,8-dimethyl-5-oxo-5,6,7,8-tetrahydro-naphthalene-2-yl)-  
18 ethynyl]phenyl]-acetic acid (**Compound 15**, General Formula 8)

19 Following general procedure J and using [2-fluoro-4-(8,8-dimethyl-5-  
20 oxo-5,6,7,8-tetrahydro-naphthalene-2-ylethynyl)phenyl]acetic acid methyl  
21 ester (**Compound 14**, 0.18g, 0.48mmol), methanol (4mL), tetrahydrofuran  
22 (8mL), water (2mL) and lithium hydroxide monohydrate (0.2g, 4.76mmol)  
23 followed by flash column chromatography over silica gel (230-400 mesh)  
24 using 50- 100% ethyl acetate in hexane as the eluent, the title compound was  
25 obtained as a dirty white solid (0.068g, 41%).

26  $^1\text{H-NMR}$  (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.41(s, 6H), 2.03(t,  $J = 6.7\text{Hz}$ , 2H), 2.74(t,  $J =$   
27 6.8Hz, 2H), 3.73(s, 2H), 7.24-7.32(m, 3H), 7.42(dd,  $J = 1.5$ , 7.9Hz, 1H), 7.56  
28 (s, 1H), 7.99(d,  $J = 7.9\text{Hz}$ , 1H), 9.40-10.00 (br s, 1H).

1 [4-(5-(Cyclopropyl-amino)-8,8-dimethyl-5,6,7,8-tetrahydro-naphthalene-2-yl-  
2 ethynyl)-2-fluoro-phenyl] acetic acid ethyl ester (Compound 16, General  
3 **Formula 4)**

4       Following general procedure G and using [2-fluoro-4-(8,8-dimethyl-5-  
5 oxo-5,6,7,8-tetrahydro-naphthalene-2-ylethynyl) phenyl]acetic acid ethyl ester  
6 (**Compound 14**, 0.258g, 0.68mmol), dichloromethane (4mL),  
7 acetonitrile(2mL), cyclopropyl amine(1mL, 14.45mmol), acetic acid (1mL)and  
8 sodium cyanoborohydride (0.266g, 4.23mmol) followed by flash column  
9 chromatography over silica gel (230-400 mesh) using 16-20-25% ethyl acetate  
10 in hexane as the eluent , the title compound was obtained as a pale yellow oil  
11 (0.21g, 73%).

12 <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>):δ 0.35-0.54 (m, 4H), 1.25(t, *J* = 7.1Hz, 3H),  
13 1.26(s, 3H), 1.32(s, 3H), 1.53-1.64(m, 1H), 1.82-2.05 (m, 3H), 2.21-2.28(m,  
14 1H), 3.65(s, 2H), 3.78(t, *J* = 5.0Hz, 1H), 4.17(q, *J* = 7.1Hz, 2H), 7.19-7.41 (m,  
15 5H), 7.47(d, *J* = 1.5Hz, 1H).

16 [4-(5-(Cyclopropyl-methyl-amino)-8,8-dimethyl-5,6,7,8-tetrahydro-  
17 naphthalene-2-yl-ethynyl)-2-fluoro-phenyl]-acetic acid ethyl ester  
18 (**Compound 17, General Formula 8)**

19       Following general procedure H and using [4-((5-cyclopropyl-amino)-  
20 8,8-dimethyl-5,6,7,8-tetrahydro-naphthalene-2ylethynyl)-2-fluoro-  
21 phenyl]acetic acid ethyl ester (**Compound 16**, 0.21g, 0.5mmol), acetone  
22 (5mL), potassium carbonate (1.13g, 8.17mmol) and methyl iodide (0.5mL,  
23 8mmol), the following work-up was used. The volatiles were distilled off in  
24 *vacuo* and the residue was diluted with water and extracted with  
25 dichloromethane (x2). The combined organic extract was dried over  
26 anhydrous sodium sulfate, filtered and evaporated in *vacuo* to afford an oil.  
27 Flash column chromatography over silica gel (230-400 mesh) using 8% ethyl  
28 acetate in hexane as the eluent afforded the title compound (0.15g, 69%).

<sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 0.39-0.53(m, 4H), 1.27(s, 3H), 1.31 (s, 3H), 1.66-1.81(m, 2H), 1.89-2.05(m, 2H), 2.08-2.13 (m, 1H), 2.13 (s, 3H), 3.62(s, 2H), 3.94 (t, *J* = 8.0Hz, 1H), 4.16(q, *J* = 7.1Hz, 2H), 7.20-7.29(m, 4H), 7.44(d, *J* = 1.5Hz, 1H), 7.51 (d, *J* = 8.2Hz, 1H).

[4-(5-(Cyclopropyl-methyl-amino)-8,8-dimethyl- 5,6,7,8-tetrahydro-naphthalene-2-yl-ethynyl)-2-fluoro-phenyl]-acetic acid (**Compound 18**, **General Formula 4**)

Following general procedure J and using [4-(5-(cyclopropyl-methyl-amino)-8,8-dimethyl- 5,6,7,8-tetrahydro-naphthalene-2-ylethynyl)-2-fluoro-phenyl]-acetic acid ethyl ester (**Compound 17**, 0.025g, 0.059mmol), methanol (1mL), tetrahydrofuran (1mL), water (0.5mL) and lithium hydroxide monohydrate (0.060g, 1.43mmol), the title compound was obtained as a white solid (0.023g, 95%).

<sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>):δ 0.52-0.54(m, 2H), 0.68-0.70(m, 2H), 1.27(s, 3H), 1.29(s, 3H), 1.63-1.80(m, 2H), 1.95-2.17(m, 2H), 2.19-2.24(m, 1H), 2.24(s, 3H), 3.60(s, 2H), 4.18(t, *J* = 7.7Hz, 1H), 7.19-7.28(m, 4H), 7.45 (d, *J* = 1.5Hz, 1H), 7.49(d, *J* = 8.2Hz, 1H), 8.80-9.20(br s, 1H).

**GENERAL PROCEDURE K: 8,8-Dimethyl-5,6,7,8-tetrahydro-naphthalene-1-one-2-carboxylic acid-4-(tert-butoxycarbonylmethyl)phenyl ester Compound 19, General Formula 8)**

A solution of 4,4-dimethyl-6-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydronaphthalene-1-one (**Intermediate 11**, 0.14g, 0.434mmol), *t*-butyl-4-hydroxy-phenyl acetate (**Reagent E**, 0.14g, 0.673mmol), palladium acetate (0.054g, 0.24mmol) and 1,3-bis(diphenylphosphino)propane (0.082g, 0.2mmol) in a mixture of dimethylsulfoxide (1mL), 1,2-dichloroethane (1.5mL) and triethyl amine (1mL) was heated at 70°C under an atmosphere of carbon monoxide overnight. The volatiles were distilled off in *vacuo* and the residue was diluted with water and extracted with diethyl ether (x3). The combined organic extract was dried over anhydrous magnesium sulfate,

1 filtered and evaporated in *vacuo* to an oil which was subjected to flash column  
2 chromatography over silica gel (230-400 mesh) using 15% ethyl acetate in  
3 hexane as the eluent to afford the title compound (0.11g, 53%).  
4 <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 1.44(s, 3H), 1.44(s, 9H), 1.46 (s, 3H), 2.07(t, *J*  
5 = 6.9Hz, 2H), 2.76(t, *J* = 6.8Hz, 2H), 3.55(s, 2H), 7.17 (d, *J* = 8.5Hz, 2H),  
6 7.35(d, *J* = 8.5Hz, 2H), 8.05-8.13(m, 2H), 8.25 (d, *J* = 1.5Hz, 1H).

7 8,8-Dimethyl-5-oxo-5,6,7,8-tetrahydro-naphthalene-2-carboxylic acid-4-  
8 (carboxymethyl)phenyl ester (Compound 20, General Formula 8)

9 A solution of 8,8-dimethyl-5-oxo-5,6,7,8-tetrahydro-naphthalene-2-  
10 carboxylic acid 4-(*tert*-butoxycarbonylmethyl)phenyl ester (Compound 19,  
11 0.11g, 0.229mmol) in dichloromethane (2mL) was treated with trifluoroacetic  
12 acid (0.85mL and stirred at ambient temperature for 2.5h. The volatiles were  
13 distilled off in *vacuo* and the residue was diluted with water and extracted with  
14 ethyl acetate (x3). The combined organic phase was dried over anhydrous  
15 sodium sulfate, filtered and evaporated in *vacuo* to afford a solid which was  
16 subjected to flash column chromatography over silica gel (230-400 mesh)  
17 using ethyl acetate as the eluent to afford the title compound (0.024g, 25%).  
18 <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 1.46 (s, 6H), 2.08(t, *J* = 6.7Hz, 2H), 2.80(t, *J*  
19 = 6.7Hz, 2H), 3.70(s, 2H), 7.20(d, *J* = 8.5Hz, 2H), 7.37(d, *J* = 8.5Hz, 2H),  
20 8.08(dd, *J* = 1.4, 8.2Hz, 1H), 8.14 (d, *J* = 8.2Hz, 1H), 8.24 (d, *J* = 1.2Hz, 1H).

21 5-Methoxy-3,3-dimethyl-indane (Intermediate 15)

22 Following general procedure A and using titanium tetrachloride  
23 (5.5mL, 50mmol), anhydrous dichloromethane (80mL), 2M solution dimethyl  
24 zinc (50mL) in toluene and a solution of 6-methoxy-indane-1-one (4.05g,  
25 25mmol) in dichloromethane (10mL) the title compound was obtained as an  
26 oil (3.13g, 71%).  
27 <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 1.37 (s, 6H), 2.04(t, *J* = 7.2Hz, 2H), 2.94(t, *J* =  
28 7.2Hz, 2H), 3.89(s, 3H), 6.82(d, *J* = 2.1Hz, 1H), 7.28(dd, *J* = 2.1, 7.0Hz, 1H),  
29 7.35 (d, *J* = 7.0Hz, 1H).

1 5-Methoxy-3,3-dimethyl-indane-1-one (Intermediate 16)

2       Following general procedure B and using 5-methoxy-3,3-dimethyl  
3 indane (**Intermediate 15**, 3.13g, 17.78mmol) in 20mL of glacial acetic acid  
4 and a solution of chromium trioxide (3.91g, 39.1mmol) in 20mL of acetic acid  
5 and 20mL of water the title compound was obtained as a viscous yellow oil  
6 (3.3g, 97%).

7 <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 1.37 (s, 6H), 2.54 (s, 2H), 3.87(s, 3H), 6.86-  
8 6.87 (m, 2H), 7.60 (d, *J* = 7.0Hz, 1H).

9 6-Methoxy-4,4-dimethyl-1,2,3,4-tetrahydro-isoquinoline-1-one (Intermediate  
10 17)

11       A solution of 5-methoxy-3,3-dimethyl-indane-1-one (**Intermediate 16**,  
12 3.3g, 17.4mmol) in benzene (50mL) was treated with concentrated sulfuric  
13 acid (10mL) and heated to 60°C. Sodium azide (1.95g, 30mmol) was added in  
14 small portions and after the addition was complete, the reaction mixture was  
15 heated further for 4h. It was then cooled, diluted with water and extracted with  
16 chloroform (x3). The combined organic phase was dried over anhydrous  
17 magnesium sulfate, filtered and evaporated in *vacuo* to afford the title  
18 compound as a brown solid (3.5g, quantitative by weight).

19 <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 1.31 (s, 6H), 3.28 (s, 2H), 3.83(s, 3H), 6.78 (d,  
20 *J* = 2.6Hz, 1H), 6.82(dd, *J* = 2.6Hz, 8.5Hz, 1H), 7.59 (s, 1H), 8.02 (d, *J* =  
21 8.2Hz, 1H).

22 6-Methoxy-4,4-dimethyl-1,2,3,4-tetrahydro-isoquinoline (Intermediate 18)

23       A solution of 6-methoxy-4,4-dimethyl-1,2,3,4-tetrahydro-isoquinoline-  
24 1-one (**Intermediate 17**, 3.5g, 17mmol) in 100mL of anhydrous  
25 tetrahydrofuran was treated with lithium aluminum hydride (1.3g,  
26 34.25mmol) in small portions and the resulting suspension was refluxed for 3  
27 hours under argon. The reaction mixture was then cooled in an ice bath and  
28 cautiously quenched with saturated aqueous sodium sulfate solution and the  
29 resulting slurry was filtered and the filter-cake washed well with ethyl acetate.

1 The filtrate and washings were evaporated in *vacuo* to a brown oil which was  
2 dissolved in chloroform, the solution was dried over anhydrous magnesium  
3 sulfate, filtered and evaporated in *vacuo* to afford the title compound (3.2g,  
4 ~100%).

5 <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 1.27 (s, 6H), 2.22 (s, 1H), 2.84 (s, 2H), 3.79 (s,  
6 3H), 3.95 (s, 2H), 6.68(dd, *J* = 2.4Hz, 8.3Hz, 1H), 6.86(d, *J* = 2.4Hz, 1H), 6.91  
7 (d, *J* = 8.3Hz, 1H).

8 6-Methoxy-4,4-dimethyl-1,2,3,4-tetrahydro-isoquinoline-2-carbaldehyde  
9 **(Intermediate 19)**

10 A solution of 6-methoxy-4,4-dimethyl-1,2,3,4-tetrahydro-isoquinoline  
11 **(Intermediate 18, 3.2g, 16.7mmol)** in anhydrous dichloromethane (40mL)  
12 was treated with formic acid (1mL, 26.5mmol) followed 1-(3-  
13 dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (3.9g, 20.34mmol)  
14 and the resulting solution was stirred at ambient temperature overnight. It was  
15 then diluted with chloroform and washed with water (x1) and brine (x1), dried  
16 over anhydrous magnesium sulfate, filtered and evaporated in *vacuo* to afford  
17 the title compound as pale brown viscous oil (3.26g, 90%).

18 <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 1.28 (s, 6H), 3.32 (s, 0.7H), 3.54 (s, 0.3H),  
19 3.79(s, 3H), 4.54 (s, 0.3H), 4.66(s, 0.7H), 6.71(dd, *J* = 2.6Hz, 8.2Hz, 1H),  
20 6.85-6.97(m, 1H), 7.02-7.27(m, 1H), 8.15(s, 0.7H), 8.34(s, 0.3H), 8.40-8.80  
21 (br s, 1H).

22 6-Hydroxy-4,4-dimethyl-1,2,3,4-tetrahydro-isoquinoline-2-carbaldehyde  
23 **(Intermediate 20)**

24 A stirred, cooled (-78°C) solution of 6-methoxy-4,4-  
25 dimethyl-1,2,3,4-tetrahydro-isoquinoline-2-carbaldehyde **(Intermediate 19,**  
26 3.26g, 15mmol) in anhydrous dichloromethane (15mL) was treated with 1M  
27 solution of boron tribromide in dichloromethane (50mL) stirred at ambient  
28 temperature for 3h. It was then cooled again to 78°C and quenched carefully  
29 with saturated aqueous sodium carbonate solution, diluted with water and the  
aqueous phase was extracted with ethyl acetate (x2). The combined organic

1 extract was dried over anhydrous sodium sulfate, filtered and evaporated in  
2 *vacuo* to afford the title compound as a solid foam (3g, 99%).

3 <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 1.23 (s, 6H), 3.31 (s, 0.7H), 3.54 (s, 0.3H),  
4 4.51 (s, 0.3H), 4.64 (s, 0.7H), 6.70-6.75(m, 1H), 6.84-6.90(m, 2H), 7.50-  
5 7.80(br s, 1H), 8.12(s, 0.7H), 8.32(s, 0.3H).

6 2-Cyclopropyl-6-hydroxy-4,4-dimethyl-1,2,3,4-tetrahydro-isoquinoline  
7 **(Intermediate 21)**

8 A stirred, cooled (0°C) solution of 6-hydroxy-4,4-dimethyl-1,2,3,4-  
9 tetrahydro-isoquinoline-2-carbaldehyde (**Intermediate 20**, 2.3g, 11.21mmol)  
10 in anhydrous tetrahydrofuran (40mL) under argon was treated with titanium  
11 tetra-*iso*-propoxide (8.28mL, 28mmol) followed by 3M solution of ethyl  
12 magnesium bromide in diethyl ether (18.7mL) and the reaction mixture was  
13 then heated at 55°C overnight. It was then cooled in an ice-bath, quenched  
14 with saturated aqueous ammonium chloride solution and extracted with diethyl  
15 ether (x2). The combined organic phase was dried over anhydrous sodium  
16 sulfate, filtered and evaporated in *vacuo* to afford a yellow oily solid. Flash  
17 column chromatography over silica gel (230-400 mesh) using 10-20% ethyl  
18 acetate in hexane as the eluent afforded the title compound as a pale yellow  
19 solid (1.55g, 63%).

20 <sup>1</sup>H-NMR (300 MHz, CD<sub>3</sub>COCD<sub>3</sub>): δ 0.016-0.16(m, 4H), 0.847 (s, 6H), 1.37  
21 (m, 1H), 2.20(s, 2H), 3.25 (s, 2H), 6.22(dd, *J* = 2.4, 8.2Hz, 1H), 6.41(d, *J* =  
22 2.6Hz, 1H), 6.47(d, *J* = 8.2Hz, 1H), 7.62(s, 1H).

23 2-Cyclopropyl-4,4-dimethyl-6-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydro-  
24 isoquinoline (**Intermediate 22**)

25 Following general procedure C and using 2-cyclopropyl-6-hydroxy-4,4-  
26 dimethyl-1,2,3,4-tetrahydro-isoquinoline (**Intermediate 21**, 1.5g, 6.9mmol) in  
27 anhydrous dichloromethane (30mL), triethyl amine (1.5mL, 10.39mmol) and  
28 [N,N'-bis(trifluoromethylsulfonyl)amino]-5-chloropyridine (2.75g, 7mmol)  
29 followed by flash column chromatography over silica gel (230-400 mesh)

1 using 8% ethyl acetate in hexane as the eluent the title compound was obtained  
2 (2.23g, 92%) as oil. <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 0.42-0.54(m, 4H), 1.25(s,  
3 6H), 1.76(m, 1H), 2.62(s, 2H), 3.74(s, 2H), 6.98(dd, *J* = 2.3, 8.4Hz, 1H),  
4 7.16(d, *J* = 8.2Hz, 1H), 7.14(d, *J* = 2.3Hz, 1H).

5 Ethyl-2-cyclopropyl-4,4-dimethyl-1,2,3,4-tetrahydroisoquinoline-6-  
6 carboxylate (Intermediate 23)

7 Following general procedure K and using 2-cyclopropyl-4,4-dimethyl-  
8 6-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydro-isoquinoline (Intermediate  
9 22, 1.6g, 4.6mmol), palladium acetate (0.127g, 0.56mmol), 1,3-  
10 bis(diphenylphosphino)propane (0.160g, 0.39mmol), dimethylsulfoxide  
11 (2mL), 1,2-dichloroethane (5mL), triethyl amine (2mL), ethanol (5mL) and an  
12 atmosphere of carbon monoxide followed by flash column chromatography  
13 over silica gel (230-400 mesh) using 10% ethyl acetate in hexane as the eluent  
14 the title compound was obtained as an oil (1g, 79%).

15 <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 0.44-0.54(m, 4H), 1.27(s, 6H), 1.38 (t, *J* =  
16 7Hz, 3H), 1.73(m, 1H), 2.62(s, 2H), 3.76(s, 2H), 4.35 (q, *J* = 7.1Hz, 2H),  
17 7.04(d, *J* = 7.9Hz, 1H), 7.74 (dd, *J* = 1.7, 7.9Hz, 1H), 7.97(d, *J* = 1.8Hz, 1H).  
18 2-Cyclopropyl-6-hydroxymethyl-4,4-dimethyl-1,2,3,4-tetrahydroisoquinoline  
19 (Intermediate 24)

20 A stirred cooled (-78°C) solution of ethyl-2-cyclopropyl-4,4-dimethyl-  
21 1,2,3,4-tetrahydro isoquinoline-6-carboxylate (Intermediate 23, 1g,  
22 3.66mmol) in anhydrous dichloromethane (20mL) under argon was treated  
23 with a 1M solution of di-*iso*-butyl aluminum hydride in dichloromethane  
24 (10mL) and the reaction mixture was warmed to -20°C over 1h. It was then  
25 quenched with saturated aqueous ammonium chloride solution and diluted  
26 with dichloromethane and filtered over a bed of celite. The phases were  
27 separated and the aqueous phase was extracted with dichloromethane (x1).  
28 The combined organic extract was dried over anhydrous sodium sulfate,



1 filtered and evaporated in *vacuo* to afford the title compound as a viscous oil  
2 (0.74g, 87%).

3 <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 0.45-0.53(m, 4H), 1.25(s, 6H), 1.72-1.82(m,  
4 2H), 2.61(s, 2H), 3.73(s, 2H), 4.61 (d, *J* = 5Hz, 2H), 6.98(d, *J* = 7.9Hz, 1H),  
5 7.07 (dd, *J* = 1.5, 7.6Hz, 1H), 7.27(s, 1H).

6 2-Cyclopropyl-4,4-dimethyl-1,2,3,4-tetrahydroisoquinoline-6-carbaldehyde  
7 **(Intermediate 25)**

8 A solution of 2-cyclopropyl-6-hydroxymethyl-4,4-dimethyl-1,2,3,4-  
9 tetrahydroisoquinoline (**Intermediate 24**, 0.74g, 3.2mmol) in dichloromethane  
10 (10mL) and acetonitrile (2.5mL) was treated sequentially with 4A<sup>0</sup> molecular  
11 sieves powder (1.06g), tetra-*n*-propyl ammonium perruthenate (0.050g,  
12 0.14mmol) and N-methyl morpholine N-oxide (1.1g, 9.8mmol). After stirring  
13 at ambient temperature for 0.5h, it was diluted with 5mL of hexane and  
14 subjected to flash column chromatography over silica gel (230-400 mesh)  
15 using 10% ethyl acetate in hexane as the eluent to afford the title compound as  
16 an oil (0.27g, 37%).

17 <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>):δ 0.44-0.56(m, 4H), 1.30(s, 6H), 1.79(m, 1H),  
18 2.66(s, 2H), 3.82(s, 2H), 7.17(d, *J* = 7.9Hz, 1H), 7.60 (dd, *J* = 1.6, 7.9Hz, 1H),  
19 7.82(d, *J* = 1.8Hz, 1H), 9.95 (s, 1H).

20 6-(2,2-Dibromo-vinyl)-2-cyclopropyl-4,4-dimethyl-1,2,3,4-  
21 tetrahydroisoquinoline (**Intermediate 26**)

22 A stirred, cooled (ice-bath) solution of triphenyl phosphine (0.53g,  
23 2mmol) in anhydrous dichloromethane was treated with carbon tetrabromide  
24 (0.35g, 1mmol) under argon. After 0.5h, a solution of 2-cyclopropyl-4,4-  
25 dimethyl-1,2,3,4-tetrahydroisoquinoline-6-carboxaldehyde (**Intermediate 25**,  
26 0.13g, 0.57mmol) in dichloromethane (2mL) was cannulated into the reaction  
27 mixture. After 1.5h between 0°C and 10°C, the reaction mixture was subjected  
28 to flash column chromatography over silica gel (230-400 mesh) using 3-5%

1 ethyl acetate in hexane as the eluent to afford the title compound as a viscous,  
2 pale yellow oil (0.18g, 82%).  
3 <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 0.49-0.57(m, 4H), 1.31(s, 6H), 1.80(m, 1H),  
4 2.67(s, 2H), 3.77(s, 2H), 7.04(d, *J* = 7.9Hz, 1H), 7.29 (dd, *J* = 1.7, 7.9Hz, 1H),  
5 7.49 (s, 1H), 7.50(d, *J* = 1.7Hz, 1H).

6 2-Cyclopropyl-6-ethynyl-4,4-dimethyl-1,2,3,4-tetrahydroisoquinoline  
7 **(Intermediate 27)**

8 A stirred, cooled (-78°C) solution of 6-(2,2-dibromo-vinyl)-2-  
9 cyclopropyl-4,4-dimethyl-1,2,3,4-tetrahydroisoquinoline-6-carboxaldehyde  
10 (**Intermediate 26**, 0.18g, 0.47mmol) in tetrahydrofuran (2mL) was treated  
11 with 1.6M solution of *n*-butyl lithium (0.6mL, 0.96mmol) under argon. The  
12 reaction mixture was allowed to warm to -20°C over 1.5h, quenched with  
13 saturated aqueous ammonium chloride solution and extracted with diethyl  
14 ether (x2). The combined organic phase was dried over anhydrous magnesium  
15 sulfate, filtered and evaporated in *vacuo* to afford the title compound as an oil  
16 (0.1g, 94%).

17 <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 0.47-0.55(m, 4H), 1.28(s, 6H), 1.77(m, 1H),  
18 2.63(s, 2H), 3.05(s, 1H), 3.67(s, 2H), 6.98(d, *J* = 7.6Hz, 1H), 7.26 (dd, *J* =  
19 1.5, 7.9Hz, 1H), 7.46(d, *J* = 1.5Hz, 1H).

20 [4-(2-Cyclopropyl-4,4-dimethyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-ethynyl]-  
21 2-fluoro-phenyl]-acetic acid ethyl ester (Compound 21, General Formula 3)

22 Following general procedure F and using 2-cyclopropyl-6-ethynyl-4,4-  
23 dimethyl-1,2,3,4-tetrahydro-isoquinoline(**Intermediate 27**, 0.13g,  
24 0.571mmol), 2-fluoro-4-iodo phenyl acetic acid ethyl ester (**Reagent C**, 0.16g,  
25 0.52mmol), triethyl amine (0.8mL), anhydrous tetrahydrofuran (2mL),  
26 copper(I)iodide (0.051g, 0.27mmol) and  
27 dichlorobis(triphenylphosphine)palladium(II) (0.1g, 0.14mmol) followed by  
28 flash column chromatography over silica gel (230-400 mesh) using 10% ethyl  
29 acetate in hexane as the eluent, 0.1g of the title compound was obtained as an

1 oil. It was further purified by preparative normal phase HPLC on a partisil-10  
2 silica column using 10% ethyl acetate in hexane as the mobile phase (0.055g,  
3 24%).

4 <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 0.42-0.51(m, 4H), 1.26(t, *J* = 7.3Hz, 3H),  
5 1.27(s, 6H), 1.75(m, 1H), 2.61(s, 2H), 3.66(s, 2H), 3.74(s, 2H), 4.18 (q, *J* =  
6 7.3Hz, 2H), 6.97 (d, *J* = 7.9Hz, 1H), 7.20-7.29(m, 4H), 7.45(d, *J* = 1.5Hz,  
7 1H).

8 [4-(2-Cyclopropyl-4,4-dimethyl-1,2,3,4-tetrahydro-isoquinolin-6-yl-ethynyl)-  
9 2-fluoro-phenyl]-acetic acid (Compound 22, General Formula 3)

10 Following general procedure J and using [4-(2-cyclopropyl-4,4-  
11 dimethyl-1,2,3,4-tetrahydro-isoquinolin-6-ylethynyl)-2-fluoro-phenyl]-acetic  
12 acid ethyl ester (**Compound 21**, 0.055g, 0.135mmol), methanol (2mL),  
13 tetrahydrofuran (4mL), water (1mL) and lithium hydroxide monohydrate  
14 (0.117g, 2.97mmol) the title compound was obtained as a pale yellow solid  
15 foam (0.040g, 78%).

16 <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 0.52-0.65(m, 4H), 1.27(s, 6H), 1.84(m, 1H),  
17 2.71(s, 2H), 3.61(s, 2H), 3.85(s, 2H), 6.98(d, *J* = 7.9Hz, 1H), 7.06 (t, *J* =  
18 7.6Hz, 1H), 7.17-7.25(m, 3H), 7.43(d, *J* = 1.2Hz, 1H), 8.60-9.00(br s, 1H).

19 [4-(2-Cyclopropyl-4,4-dimethyl-1,2,3,4-tetrahydro-isoquinolin-6-yl-ethynyl)-  
20 phenyl]-acetic acid methyl ester (Compound 23, General Formula 3)

21 Following general procedure F and using 2-cyclopropyl-4,4-dimethyl-  
22 6-ethynyl-1,2,3,4-tetrahydro-isoquinoline(**Intermediate 27**, 0.13g,  
23 0.571mmol), 4-iodo phenyl acetic acid methyl ester (**Reagent B**, 0.16g,  
24 0.58mmol), triethyl amine (0.5mL), anhydrous tetrahydrofuran (2mL),  
25 copper(I)iodide (0.04g, 0.21mmol) and  
26 dichlorobis(triphenylphosphine)palladium(II) (0.12g, 0.17mmol) followed by  
27 flash column chromatography over silica gel (230-400 mesh) using 10% ethyl  
28 acetate in hexane as the eluent, 0.05g of the title compound was obtained as an  
29 oil. It was further purified by preparative normal phase HPLC on a partisil-10

1 silica column using 10% ethyl acetate in hexane as the mobile phase (0.01g,  
2 6%).  
3 <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 0.42-0.58(m, 4H), 1.29(m, 6H), 1.79(m, 1H),  
4 2.64(s, 2H), 3.67(s, 3H), 3.72(s, 2H), 3.77(s, 2H), 7.09 (d, *J* = 7.9Hz, 1H),  
5 7.28(dd, *J* = 1.5, 7.9Hz, 1H), 7.36 (d, *J* = 7.9Hz, 2H), 7.50 (d, *J* = 1.6Hz, 1H),  
6 7.51(d, *J* = 7.9Hz, 2H).

7 [4-(2-Cyclopropyl-4,4-dimethyl-1,2,3,4-tetrahydro-isoquinolin-6-yl-ethynyl)-  
8 phenyl]-acetic acid (Compound 24, General Formula 3)

9       Following general procedure J and using [4-(2-cyclopropyl-4,4-  
10 dimethyl-1,2,3,4-tetrahydro-isoquinolin-6ylethynyl)-phenyl]-acetic acid  
11 methyl ester (**Compound 23**, 0.01g, 0.027mmol), methanol (1mL),  
12 tetrahydrofuran (1mL), water (0.5mL) and lithium hydroxide monohydrate  
13 (0.042g, 1mmol) the title compound was obtained as a pale yellow solid foam  
14 (0.0065g, 68%).

15 <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 0.35-0.52(m, 4H), 1.24(s, 6H), 1.74(m, 1H),  
16 2.59(s, 2H), 3.64(s, 2H), 3.71(s, 2H), 7.03 (d, *J* = 8.2Hz, 1H), 7.22(dd, *J* =  
17 1.4, 7.9Hz, 1H), 7.33 (d, *J* = 8.2Hz, 2H), 7.46 (d, *J* = 8.2Hz, 2H), 7.47(s, 1H).  
18 1-(Iso-propyl-methyl-amino)-6-trimethylsilanylethynyl-4,4-dimethyl-1,2,3,4-  
19 tetrahydro-naphthalene (Intermediate 28)

20       Following general procedure G and using a solution of 4,4-dimethyl-6-  
21 trimethylsilanylethynyl-1,2,3,4-tetrahydro-naphthalene 2-one (**Intermediate**  
22 **12**, 0.2g, 0.78mmol), dichloromethane (4mL), acetonitrile (2mL), acetic acid  
23 (1mL), isopropyl amine (1mL, 11.74mmol) and sodium cyanoborohydride  
24 (0.19g, 3.02mmol), after 15days of reaction time and work up afforded an  
25 intermediate (0.14g, 60%, 0.47mmol) which was used following general  
26 procedure H along with acetone (2mL), potassium carbonate (0.6g, 4.34mmol)  
27 and methyl iodide (0.5mL, 8mmol). The crude product after work up was  
28 subjected to flash column chromatography over silica gel (230-400 mesh)

1 using 15% ethyl acetate in hexane as the eluent to afford the title compound as  
2 a pale yellow oil (0.14g, 95%).

3 <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 0.001(s, 9H), 0.85 (d, *J* = 6.4Hz, 6H), 0.98 (s,  
4 3H), 1.03 (s, 3H), 1.32-1.60 (m, 4H), 1.81(s, 3H), 2.64(heptet, *J* = 6.4Hz, 1H),  
5 3.65 (dd, *J* = 6.1, 9.4Hz, 1H), 6.97 (dd, *J* = 1.7, 7.9Hz, 1H), 7.13 (d, *J* =  
6 1.7Hz, 1H), 7.82 (d, *J* = 7.9Hz, 1H).

7 6-Ethynyl-1-(*iso*-propyl-methyl-amino)-4,4-dimethyl-1,2,3,4-tetrahydro-  
8 naphthalene (Intermediate 29)

9 Following general procedure E and using 1-(methyl-*iso*-propylamino)-  
10 4,4-dimethyl-6-trimethylsilanylethynyl-1,2,3,4-tetrahydro-naphthalene  
11 (Intermediate 28, 0.14g, 0.45mmol), methanol (5mL), potassium carbonate  
12 (0.61g, 4.41mmol) and ethyl acetate the title compound (0.092g, 80%) was  
13 obtained as an oil.

14 <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 1.11(d, *J* = 6.4Hz, 6H), 1.23(s, 3H), 1.28(s,  
15 3H), 1.51-1.87 (m, 4H), 2.09(s, 3H), 2.90 (heptet, *J* = 6.4Hz, 1H), 3.00(s, 1H),  
16 3.91 (dd, *J* = 5.8, 10.0Hz, 1H), 7.25(dd, *J* = 1.7, 8.2Hz, 1H), 7.41 (d, *J* =  
17 1.7Hz, 1H), 7.70(d, *J* = 8.2Hz, 1H).

18 4-[5-(*Is*o-propyl-methyl-amino)-8,8-dimethyl-5,6,7,8-tetrahydro-naphthalene-  
19 2-yl-ethynyl]-benzoic acid ethyl ester (Compound 25, General Formula 4)

20 Following general procedure F and 6-ethynyl-1-(*iso*-propyl-methyl-  
21 amino)-4,4-dimethyl-1,2,3,4-tetrahydro-naphthalene (Intermediate 29,  
22 0.092g, 0.36mmol), ethyl-4-iodo benzoate (Reagent A, 0.12g, 0.48mmol),  
23 triethyl amine (1mL), tetrahydrofuran (2mL), copper(I)iodide (0.028g,  
24 0.14mmol) and dichlorobis(triphenylphosphine)palladium(II) (0.075g,  
25 0.11mmol) followed by flash column chromatography over silica gel (230-400  
26 mesh) using 10-15% ethyl acetate in hexane as the eluent the title compound  
27 was obtained (0.04g, 27%).

28 <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 1.12 (d, *J* = 6.5Hz, 6H), 1.27 (s, 3H), 1.31 (s,  
29 3H), 1.40 (t, *J* = 7.0Hz, 3H), 1.62-1.89 (m, 4H), 2.10(s, 3H), 2.92 (heptet, *J* =

1 6.4Hz, 1H), 3.94(dd,  $J = 6.1, 9.7$ Hz, 1H), 4.38(q,  $J = 7.1$ Hz, 2H), 7.31(dd,  $J =$   
2 1.4, 8.2Hz, 1H), 7.46 (d,  $J = 1.7$ Hz, 1H), 7.58 (d,  $J = 8.2$ Hz, 2H), 7.75(d,  $J =$   
3 8.2Hz, 1H), 8.01(d,  $J = 8.2$ Hz, 2H).

4 4-[5-(*Iso*-propyl-methyl-amino)-8,8-dimethyl-5,6,7,8-tetrahydro-naphthalene-  
5 2-yl-ethynyl)]-benzoic acid (Compound 26, General Formula 4)

6 Following general procedure I and using 4-[5-(*iso*-propyl-methyl-  
7 amino)-8,8-dimethyl-5,6,7,8-tetrahydro-naphthalene-2-ylethynyl)]-benzoic  
8 acid ethyl ester (Compound 25, 0.04g, 0.01mmol), ethanol (2mL),  
9 tetrahydrofuran (1mL) and 1M aqueous sodium hydroxide solution (1mL)  
10 followed by recrystallization from diethylether-hexane, the title compound  
11 was obtained as an off-white solid (0.010g, 27%).  
12 <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  1.30(d,  $J = 6.0$ Hz, 6H), 1.31(s, 9H), 1.67-  
13 1.98(m, 4H), 2.35 (s, 3H), 3.19 (heptet,  $J = 6.4$ Hz, 1H), 4.36 (t,  $J = 7.6$ Hz,  
14 1H), 7.28(dd,  $J = 1.4, 8.2$ Hz, 1H), 7.48 (d,  $J = 1.4$ Hz, 1H), 7.55 (d,  $J = 8.2$ Hz,  
15 2H), 7.81 (d,  $J = 8.2$ Hz, 1H), 8.05 (d,  $J = 8.2$ Hz, 2H).

16 [4-(2,2,4,4-Tetramethyl-chroman-6-yl-ethynyl) phenyl] acetic acid methyl  
17 ester (Compound 27, General Formula 8)

18 Following general procedure F and using 6-ethynyl-2,2,4,4-  
19 tetramethylchroman (synthesis described in U.S. Patent Nos. 5,045,551 and  
20 5,616,597 incorporated herein by reference) (0.060g, 0.28mmol), methyl-4-  
21 iodo phenyl acetate (Reagent B, 0.078g, 0.28mmol), triethyl amine (4mL),  
22 tetrahydrofuran (4mL), copper(I)iodide (0.030g, 0.16mmol) and  
23 dichlorobis(triphenylphosphine)palladium(II) (0.11g, 0.16mmol) followed by  
24 flash column chromatography over silica gel (230-400 mesh) using 5-10 %  
25 ethyl acetate in hexane as the eluent the title compound was obtained (0.047g,  
26 46%).

27 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  7.48-7.45 (m, 3H), 7.25-7.23 (m, 3H), 6.75 (d,  
28 1H,  $J = 8.2$ Hz), 3.70 (s, 3H), 3.62 (s, 2H), 1.84 (s, 2H), 1.36 (s, 6H), 1.35 (s,  
29 6H).

1 GENERAL PROCEDURE L: [4-(2,2,4,4-Tetramethyl-chroman-6-yl-ethynyl)  
2 phenyl] acetic acid (Compound 28, General Formula 8)

3 A solution of [4-(2,2,4,4-tetramethyl-chroman-6-yl-ethynyl) phenyl]  
4 acetic acid methyl ester (Compound 27, 0.047g, 0.13mmol) in 5mL of  
5 methanol was treated with 1M sodium hydroxide solution (2mL) and heated at  
6 55°C for 2h. The volatiles were distilled off in *vacuo* and the residue was  
7 acidified with 10% hydrochloric acid and extracted with ethyl acetate (x2).  
8 The combined organic phase was washed with brine (x1), dried over  
9 anhydrous sodium sulfate, filtered and evaporated in *vacuo* to a residue which  
10 was purified by preparative reverse phase HPLC using 10% water in  
11 acetonitrile as the mobile phase to afford the title compound (0.034g, 82%). <sup>1</sup>H  
12 NMR (300 MHz, CDCl<sub>3</sub>): δ 7.49-7.45 (m, 3H), 7.26-7.22 (m, 3H), 6.75 (d,  
13 1H, *J* = 8.2Hz), 3.65 (s, 2H), 1.84 (s, 2H), 1.36 (s, 6H), 1.35 (s, 6H).

14 2-Fluoro-4-(2,2,4,4-tetramethyl-chroman-6-yl-ethynyl)-benzoic acid methyl  
15 ester (Compound 29, General Formula 8)

16 Following general procedure F and using 6-ethynyl-2,2,4,4-  
17 tetramethylchroman (0.11g, 0.51mmol), methyl-2-fluoro-4-iodo-benzoate  
18 (Reagent G, 0.14g, 0.51mmol), triethyl amine (5mL), tetrahydrofuran(10mL),  
19 copper(I)iodide(0.030g, 0.16mmol) and  
20 dichlorobis(triphenylphosphine)palladium(II) (0.110g, 0.16mmol) followed by  
21 flash column chromatography over silica gel (230-400 mesh) using 5-10 %  
22 ethyl acetate in hexane as the eluent, the title compound was obtained (0.14g,  
23 79%).

24 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.82 (t, 1H, *J* = 7.9Hz), 7.39 (d, 1H, *J* =  
25 1.8Hz), 7.25-7.16 (m, 3H), 6.69 (d, 1H, *J* = 8.2Hz), 3.85 (s, 3H), 1.77 (s, 2H),  
26 1.29 (s, 6H), 1.28 (s, 6H).

27 2-Fluoro-4-(2,2,4,4-tetramethyl-chroman-6-yl-ethynyl)-benzoic acid  
28 (Compound 30, General Formula 8)

1       Following general procedure L and using 2-fluoro-4-(2,2,4,4-  
2 tetramethyl-chroman-6-yl-ethynyl)-benzoic acid methyl ester (**Compound 29**,  
3 0.14g, 0.4mmol), 5mL of methanol and 1M sodium hydroxide solution (2mL)  
4 followed by recrystallization from ethyl acetate, the title compound was  
5 obtained (0.083g, 58%).

6 <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>COCD<sub>3</sub>): δ 8.00 (t, 1H, *J* = 7.8Hz), 7.63 (d, 1H, *J* =  
7 2.1Hz), 7.45 (dd, 1H, *J* = 1.5, 7.9Hz), 7.38 (dd, 1H, *J* = 1.5, 11.4Hz), 7.32 (dd,  
8 1H, *J* = 2.1, 8.2Hz), 6.81 (d, 1H, *J* = 8.5Hz), 1.92 (s, 2H), 1.41 (s, 6H), 1.38 (s,  
9 6H).

10 [2-Fluoro-4-(2,2,4,4-tetramethyl-chroman-6-yl-ethynyl) phenyl] acetic acid  
11 ethyl ester (**Compound 31, General Formula 8**)

12       Following general procedure F and using 6-ethynyl-2,2,4,4-  
13 tetramethylchroman (0.204g, 0.95mmol), ethyl-2-fluoro-4-iodo phenyl acetate  
14 (**Reagent C**, 0.263g, 0.86mmol), triethyl amine, tetrahydrofuran,  
15 copper(I)iodide (0.025g, 0.13mmol) and  
16 dichlorobis(triphenylphosphine)palladium(II) (0.075g, 0.11mmol) followed by  
17 flash column chromatography over silica gel (230-400 mesh) using 5-10 %  
18 ethyl acetate in hexane as the eluent, the title compound was obtained (0.21g,  
19 62%).

20 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.46 (d, 1H, *J* = 2.1Hz), 7.25-7.21 (m, 4H),  
21 6.69 (d, 1H, *J* = 8.5Hz), 4.16 (q, 2H, *J* = 7.1Hz), 3.65 (s, 2H), 1.82 (s, 2H),  
22 1.35 (s, 6H), 1.35 (s, 6H), 1.24 (t, 3H, *J* = 7.2Hz).

23 [2-Fluoro-4-(2,2,4,4-tetramethyl-chroman-6-yl-ethynyl) phenyl] acetic acid  
24 (**Compound 32, General Formula 8**)

25       Following general procedure L and using [2-fluoro-4-(2,2,4,4-  
26 tetramethyl-chroman-6-ylethynyl) phenyl] acetic acid ethyl ester (**Compound**  
27 **31**, 0.21g, 0.58mmol), 5mL of methanol and 1M sodium hydroxide solution  
28 (2mL) followed by flash column chromatography over silica gel (230-400



1 mesh) using 50% ethyl acetate in hexane, the title compound was obtained as a  
2 solid (0.184g, 93%).

3 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 11.40 (br s, 1H), 7.48 (d, 1H, *J* = 1.8Hz), 7.46-  
4 7.16 (m, 4H), 6.76 (d, 1H, *J* = 8.2Hz), 3.69 (s, 2H), 1.82 (s, 2H), 1.34 (s, 12H).

5 3-Methyl-but-2-enoic acid 4-bromo-phenyl ester:

6 To a stirred, cooled (ice bath) suspension of sodium hydride (2.4g,  
7 100mmol) in anhydrous tetrahydrofuran (200mL), 4-bromo phenol (17.3g,  
8 100mmol) was added followed by 3,3,-dimethyl acryloyl chloride (11.14mL,  
9 100mmol). After 4hours at ambient temperature, the reaction mixture was  
10 poured into brine and extracted with diethyl ether (x2). The combined organic  
11 phase was dried over anhydrous sodium sulfate, filtered and evaporated in  
12 *vacuo* to afford an oil which was subjected to flash column chromatography  
13 over silica gel (230-400 mesh) using 2% ethyl acetate in hexane as the eluent  
14 to afford the title compound (15g, 59%).

15 <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>):δ 2.00(s, 3H), 2.23(s, 3H), 5.89(s, 1H), 7.00(d, *J*  
16 = 8.8Hz, 2H), 7.49(d, *J* = 8.8Hz, 2H).

17 6-Bromo-4,4-dimethyl-chroman-2-one:

18 A solution of 3-methyl-but-2-enoic acid 4-bromo-phenyl ester (7g,  
19 27.6mmol) in anhydrous dichloromethane (200mL) was cooled (ice bath) and  
20 treated with aluminum chloride (6.6g, 49.6mmol) and the reaction mixture was  
21 stirred overnight at ambient temperature. The reaction mixture was quenched  
22 with saturated aqueous sodium bicarbonate solution and extracted with diethyl  
23 ether (x2). The combined organic extract was washed with brine (x1), dried  
24 over anhydrous sodium sulfate, filtered and evaporated in *vacuo* to afford an  
25 oil which was purified by flash column chromatography over silica gel (230-  
26 400 mesh) using 2.5% ethyl acetate in hexane as the eluent to afford the title  
27 compound (4.2g, 57%).

28 <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>):δ 1.36(s, 6H), 2.62(s, 2H), 6.95(d, *J* = 8.5Hz,  
29 1H), 7.37(dd, *J* = 2.4, 8.5Hz, 1H), 7.43(d, *J* = 2.3Hz, 1H).

1 4-Bromo-2-(3-hydroxy-1,1,3-trimethyl-butyl)-phenol:

2 A solution of 6-bromo-4,4-dimethyl-chroman-2-one (1g, 3.92mmol) in  
3 anhydrous tetrahydrofuran (20mL) was treated with 3M solution of ethyl  
4 magnesium bromide (2.6mL) and stirred at ambient temperature for 2hours.  
5 The reaction mixture was poured into cold dilute hydrochloric acid and  
6 extracted with ethyl acetate (x2). The combined organic extract was dried  
7 over anhydrous sodium sulfate, filtered and evaporated in *vacuo* to afford a  
8 residue which was subjected to flash column chromatography over silica gel  
9 (230-400 mesh) using 10% ethyl acetate in hexane as the eluent to afford the  
10 title compound as a pale yellow solid (1.1g, 100%).

11 <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>):δ 1.14(s, 6H), 1.44(s, 6H), 2.20(s, 2H), 6.49(d, *J*  
12 = 8.4Hz, 1H), 7.15(dd, *J* = 2.4, 8.5Hz, 1H), 7.37(d, *J* = 2.4Hz, 1H).

13 6-Bromo-2,2,4,4-tetramethyl-chroman:

14 A solution of 4-bromo-2-(3-hydroxy-1,1,3-trimethyl-butyl)-phenol  
15 (1.1g, 3.92mmol) and *p*-toluene sulfonic acid (0.744g, 3.92mmol) in benzene  
16 (20mL) was refluxed overnight. The reaction mixture cooled to ambient  
17 temperature, filtered on silica gel and washed with 10% ethyl acetate in  
18 hexane. The filtrate and washings were evaporated in *vacuo* to an oil which  
19 was subjected to flash column chromatography over silica gel (230-400 mesh)  
20 using 5% ethyl acetate in hexane as the eluent to afford the title compound as a  
21 pale yellow oil (0.84g, 80%).

22 <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>):δ 1.34(s, 6H), 1.35(s, 6H), 1.82(s, 2H), 6.68(d, *J*  
23 = 8.4Hz, 1H), 7.16(dd, *J* = 2.7, 8.7Hz, 1H), 7.37(d, *J* = 2.6Hz, 1H).

24 The synthesis of this compound, as described here, is in close analogy  
25 to the synthesis of 6-bromo-2,2,4,4-tetramethylthiochroman, as described in  
26 United States Patent No. 5,045,551

27 2,2,4,4-tetramethyl-6-(2-trimethylsilyl)ethynyl chroman:

28 Following general procedure D and using 6-bromo-2,2,4,4-tetramethyl  
29 chroman (0.5g, 1.87mmol), triethyl amine (5mL), anhydrous tetrahydrofuran

1 (15mL), copper(I)iodide (0.107g, 0.156mmol), trimethylsilyl acetylene (1.84g,  
2 18.7mmol) and dichlorobis(triphenylphosphine)palladium(II) (0.39g,  
3 0.56mmol) the title compound was obtained as a brown oil (0.61g, 100%).  
4 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.43 (d, 1H, *J* = 2.1Hz), 7.23 (dd, 1H, *J* = 7.9,  
5 2.1Hz), 6.73 (d, 1H, *J* = 8.2Hz), 1.83 (s, 2H), 1.36 (s, 12H), 0.28 (s, 9H).

6 6-Ethynyl-2,2,4,4-tetramethyl chroman:

7 Following general procedure E and using 2,2,4,4-tetramethyl-6-(2-  
8 trimethylsilyl)ethynyl chroman (0.61g, 1.87mmol), potassium carbonate (1.9g,  
9 13.74mmol) and methanol the title compound was obtained (0.4g, 90%).  
10 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.47 (d, 1H, *J* = 2.1Hz), 7.24 (dd, 1H, *J* = 7.9,  
11 2.1Hz), 6.76 (d, 1H, *J* = 8.2Hz), 3.01 (s, 1H), 1.85 (s, 2H), 1.37 (s, 6H), 1.36  
12 (s, 6H).

13 An alternative synthesis for this compound is described in United States  
14 Patent Nos. 5,045,551 and 5,616,597

15 GENERAL PROCEDURE M: 6-Bromo-2,2,4,4-tetramethyl-chroman-8-  
16 carbaldehyde (Intermediate 30)

17 A stirred, cooled (ice bath) solution of 6-bromo-2,2,4,4-tetramethyl  
18 chroman, (0.5g, 1.865mmol) in anhydrous dichloromethane (5mL) was treated  
19 with a 1M solution (1.86mL, 1.86mmol) of titanium tetrachloride in  
20 dichloromethane followed by α,α-dichloro methyl ether (0.214g, 1.865mmol).  
21 The reaction mixture was allowed to warm to ambient temperature for 4h. The  
22 reaction mixture was diluted with diethyl ether, washed with brine (x1) and  
23 dried over anhydrous sodium sulfate, filtered and evaporated in *vacuo* to a  
24 residue which was subjected to flash column chromatography over silica gel  
25 (230-400 mesh) using 5% ethyl acetate in hexane to afford the title compound  
26 as a yellow solid (0.52g, 94%).  
27 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 10.38 (s, 1H), 7.72 (d, 1H, *J* = 2.6Hz), 7.57 (d,  
28 1H, *J* = 2.6Hz), 1.88 (s, 2H), 1.41 (s, 6H), 1.36 (s, 6H).

1 GENERAL PROCEDURE N: 6-Bromo-8-vinyl-2,2,4,4-tetramethyl-chroman  
2 (**Intermediate 31**)

3 A solution of methyldiene triphenyl phosphorane [generated from  
4 methyl triphenylphosphonium bromide (7g, 20mmol) and (11.8mL, 19mmol)  
5 of a 1.6M solution of *n*-butyl lithium in hexanes ] was added 6-bromo-2,2,4,4-  
6 tetramethyl chroman-8-carbaldehyde (**Intermediate 30**, 0.52g, 1.75mmol).  
7 After 1h the reaction mixture was diluted with hexane, washed with brine (x1),  
8 dried over anhydrous sodium sulfate, filtered and evaporated in *vacuo* to a  
9 clear oil which was subjected to flash column chromatography over silica gel  
10 (230-400 mesh) using 2% ethyl acetate in hexane as the eluent to afford the  
11 title compound as a clear oil (0.37g, 72%).

12 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.46 (d, 1H, *J* = 2.5Hz), 7.33 (d, 1H, *J* =  
13 2.5Hz), 7.03 (dd, 1H, *J* = 11.3, 17.9Hz), 5.75 (dd, 1H, *J* = 1.4, 17.9Hz), 5.30  
14 (dd, 1H, *J* = 1.4, 11.3Hz), 1.85 (s, 2H), 1.39 (s, 6H), 1.37 (s, 6H).

15 GENERAL PROCEDURE O: 6-Bromo-8-cyclopropyl-2,2,4,4-tetramethyl  
16 chroman (**Intermediate 32**)

17 A stirred, cooled (-30°C) solution of 6-bromo-8-vinyl-2,2,4,4-  
18 tetramethyl chroman (**Intermediate 31**, 0.37g, 1.26mmol) in diethyl ether was  
19 treated with a solution of diazomethane in diethyl ether and catalytic amount  
20 of palladium (II)acetate (~30mg). The reaction mixture was allowed to warm  
21 to ambient temperature and subjected to flash column chromatography over  
22 silica gel (230-400 mesh) using 2% ethyl acetate in hexane as the eluent to  
23 afford the title compound as a clear, pale yellow oil (0.376g, 97%).

24 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.17 (d, 1H, *J* = 2.3Hz), 6.73 (d, 1H, *J* =  
25 2.6Hz), 2.19-2.16 (m, 1H), 1.83 (s, 2H), 1.37 (s, 6H), 1.33 (s, 6H), 0.94-0.88  
26 (m, 2H), 0.64-0.59 (m, 2H).

27 8-Cyclopropyl-6-trimethylsilanylethynyl-2,2,4,4-tetramethyl chroman  
28 (**Intermediate 33**)

1       Following general procedure D and using 6-bromo-8-cyclopropyl-  
2 2,2,4,4-tetramethyl chroman (**Intermediate 32**, 0.376g, 1.22mmol),  
3 (trimethylsilyl)acetylene (4mL, 28mmol), triethyl amine (3mL), anhydrous  
4 tetrahydrofuran (5mL), copper(I)iodide (0.025g, 0.13mmol) and  
5 dichlorobis(triphenylphosphine)palladium(II) (0.075g, 0.11mmol), the title  
6 compound was obtained as an oil (0.173g, 43%).

7 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.36 (d, 1H, *J* = 2.2Hz), 6.90 (d, 1H, *J* =  
8 1.9Hz), 2.31-2.22 (m, 1H), 1.96 (s, 2H), 1.49 (s, 6H), 1.46 (s, 6H), 1.05-0.88  
9 (m, 2H), 0.78-0.72 (m, 2H), 0.37 (s, 9H).

10 8-Cyclopropyl-6-ethynyl-2,2,4,4-tetramethyl chroman (**Intermediate 34**)

11       Following general procedure E and using 8-cyclopropyl-6-  
12 trimethylsilanylethynyl-2,2,4,4-tetramethyl chroman (**Intermediate 33**, 0.17g,  
13 0.68mmol), methanol and potassium carbonate (0.2g, 1.47mmol) the title  
14 compound was obtained as an oil (0.064g, 47%).

15 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.38 (d, 1H, *J* = 1.9Hz), 6.92 (d, 1H, *J* =  
16 1.9Hz), 3.08 (s, 1H), 2.32-2.23 (m, 1H), 1.96 (s, 2H), 1.50 (s, 6H), 1.46 (s,  
17 6H), 1.05-0.99 (m, 2H), 0.77-0.72 (m, 2H).

18 4-(8-Cyclopropyl-2,2,4,4-tetramethyl-chroman-6-yl-ethynyl)-benzoic acid  
19 ethyl ester (**Compound 33, General Formula 8**)

20       Following general procedure F and using 8-cyclopropyl-6-ethynyl-  
21 2,2,4,4-tetramethylchroman (**Intermediate 34**, 0.1g, 0.38mmol), ethyl-4-iodo-  
22 benzoate (**Reagent A**, 0.1g, 0.34mmol), triethyl amine (5mL),  
23 tetrahydrofuran(10mL), copper(I)iodide(0.025g, 0.13mmol) and  
24 dichlorobis(triphenylphosphine)palladium(II) (0.075g, 0.11mmol) followed by  
25 flash column chromatography over silica gel (230-400 mesh) using 5-10 %  
26 ethyl acetate in hexane as the eluent, the title compound was obtained (0.135g,  
27 89%).

28 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 8.00 (d, 2H, *J* = 8.2Hz), 7.55 (d, 2H, *J* =  
29 8.2Hz), 7.30 (d, 1H, *J* = 1.8Hz), 6.84 (d, 1H, *J* = 2.0Hz), 4.38 (q, 2H, *J* =

1 6.9Hz), 2.22-2.12 (m, 1H), 1.85 (s, 2H), 1.40 (t, 3H,  $J = 6.9\text{Hz}$ ), 1.38 (s, 6H),  
2 1.36 (s, 6H), 0.92-0.88 (m, 2H), 0.67-0.62 (m, 2H).

3 4-(8-Cyclopropyl-2,2,4,4-tetramethyl-chroman-6-yl-ethynyl)-benzoic acid  
4 **(Compound 34, General Formula 8)**

5 Following general procedure L and using 4-(8-cyclopropyl-2,2,4,4-  
6 tetramethyl-chroman-6-yl-ethynyl)-benzoic acid ethyl ester (**Compound 33**,  
7 0.135g, 0.34mmol), 5mL of methanol and 1M sodium hydroxide solution  
8 (2mL) followed by preparative reverse phase HPLC using 10% water in  
9 acetonitrile as the mobile phase, the title compound was obtained as a solid  
10 (0.093g, 73%).

11  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  11.26 (br s, 1H), 8.08 (d, 2H,  $J = 8.2\text{Hz}$ ), 7.59  
12 (d, 2H,  $J = 8.2\text{Hz}$ ), 7.31 (d, 1H,  $J = 1.8\text{Hz}$ ), 6.85 (d, 1H,  $J = 2.1\text{Hz}$ ), 2.22-2.13  
13 (m, 1H), 1.85 (s, 2H), 1.38 (s, 6H), 1.36 (s, 6H), 0.95-0.87 (m, 2H), 0.68-0.63  
14 (m, 2H).

15 [4-(8-Cyclopropyl-2,2,4,4-tetramethyl-chroman-6-yl-ethynyl) phenyl] acetic  
16 acid methyl ester (**Compound 35, General Formula 8**)

17 Following general procedure F and using 8-cyclopropyl-6-ethynyl-  
18 2,2,4,4-tetramethylchroman (**Intermediate 34**, 0.096g, 0.38mmol), methyl-4-  
19 iodo phenyl acetate (**Reagent B**, 0.094g, 0.34mmol), triethyl amine (3mL),  
20 tetrahydrofuran (3mL), copper(I)iodide (0.025g, 0.13mmol) and  
21 dichlorobis(triphenylphosphine)palladium(II) (0.075g, 0.11mmol) the title  
22 compound was obtained (0.137g, 90%).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.47  
23 (d, 2H,  $J = 7.9\text{Hz}$ ), 7.29 (d, 1H,  $J = 1.8\text{Hz}$ ), 7.24 (d, 2H,  $J = 7.9\text{Hz}$ ), 6.82 (d,  
24 1H,  $J = 2.1\text{Hz}$ ), 3.70 (s, 3H), 3.63 (s, 2H), 2.22-2.13 (m, 1H), 1.85 (s, 2H),  
25 1.38 (s, 6H), 1.36 (s, 6H), 0.94-0.86 (m, 2H), 0.68-0.63 (m, 2H).

26 [4-(8-Cyclopropyl-2,2,4,4-tetramethyl-chroman-6-yl-ethynyl) phenyl] acetic  
27 acid (**Compound 36, General Formula 8**)

28 Following general procedure L and using [4-(8-cyclopropyl-2,2,4,4-  
29 tetramethyl-chroman-6-ylethynyl) phenyl] acetic acid methyl ester

1 (Compound 35, 0.137g, 0.30mmol), 5mL of methanol and 1M sodium  
2 hydroxide solution (2mL) followed by preparative reverse phase HPLC using  
3 10% water in acetonitrile as the mobile phase, the title compound was  
4 obtained as a solid (0.11g, 80%).  
5 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 11.56 (br s, 1H), 7.47 (d, 2H, *J* = 8.9Hz), 7.28  
6 (d, 1H, *J* = 1.9Hz), 7.23 (d, 2H, *J* = 8.5Hz), 6.82 (d, 1H, *J* = 1.9Hz), 3.62 (s,  
7 2H), 2.21-2.12 (m, 1H), 1.83 (s, 2H), 1.36 (s, 6H), 1.34 (s, 6H), 0.93-0.82 (m,  
8 2H), 0.72-0.62 (m, 2H).

9 [4-(8-Cyclopropyl-2,2,4,4-tetramethyl-chroman-6-yl-ethynyl)-2-fluorophenyl]  
10 acetic acid ethyl ester (Compound 37, General Formula 8)

11 Following general procedure F and using 8-cyclopropyl-6-ethynyl-  
12 2,2,4,4-tetramethylchroman (Intermediate 34, 0.096g, 0.38mmol), ethyl-2-  
13 fluoro-4-iodo phenyl acetate (Reagent C, 0.104g, 0.34mmol), triethyl amine  
14 (3mL), tetrahydrofuran (3mL), copper(I)iodide (0.020g, 0.1mmol) and  
15 dichlorobis(triphenylphosphine)palladium(II) (0.060g, 0.085mmol) the title  
16 compound was obtained (0.14g, 85%).  
17 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.31 (d, 1H, *J* = 1.9Hz), 7.29-7.21 (m, 3H),  
18 6.85 (d, 1H, *J* = 1.9Hz), 4.20 (q, 2H, *J* = 7.1Hz), 3.68 (s, 2H), 2.24-2.14 (m,  
19 1H), 1.87 (s, 2H), 1.40 (s, 6H), 1.38 (s, 6H), 1.28 (t, 3H, *J* = 7.1Hz), 0.96-0.85  
20 (m, 2H), 0.70-0.64 (m, 2H).

21 [4-(8-Cyclopropyl-2,2,4,4-tetramethyl-chroman-6-yl-ethynyl)-2-fluorophenyl]  
22 acetic acid (Compound 38, General Formula 8)

23 Following general procedure L and using [4-(8-cyclopropyl-2,2,4,4-  
24 tetramethyl-chroman-6-yl-ethynyl)-2-fluorophenyl] acetic acid ethyl ester  
25 (Compound 37, 0.14g, 0.323mmol), 5mL of methanol and 1M sodium  
26 hydroxide solution (2mL) followed by reverse phase HPLC using 10% water  
27 in acetonitrile as the mobile phase, the title compound was obtained as a solid  
28 (0.110g, 80%).

1 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.28 (d, 1H, *J* = 2.1Hz), 7.27-7.17 (m, 3H),  
2 6.82 (d, 1H, *J* = 1.8Hz), 3.70 (s, 2H), 2.21-2.11 (m, 1H), 1.84 (s, 2H), 1.37 (s,  
3 6H), 1.35 (s, 6H), 0.94-0.87 (m, 2H), 0.67-0.62 (m, 2H).

4 GENERAL PROCEDURE P: 6-Bromo-4,4-dimethyl-2-methylene chroman  
5 (**Intermediate 35**)

6 A stirred, cooled (ice bath) solution of 6-bromo-4,4-dimethyl-chroman-  
7 2-one available in accordance with U.S. Patent No. 5,399,561 incorporated  
8 herein by reference (1g, 3.92mmol) in 8mL of anhydrous tetrahydrofuran was  
9 treated with a 0.5 M solution of μ-chloro-μ-methylene-  
10 [bis(cyclopentadienyl)titanium]dimethylaluminum (Tebbe reagent) in toluene  
11 (8.23mL, 4.12mmol). After 10 minutes, the reaction mixture was poured into  
12 ice-water mixture containing 50mL of 1M sodium hydroxide and extracted  
13 with hexane. The hexane extract was washed with brine (x1), filtered over a  
14 bed of celite and evaporated in *vacuo* to an oil which was subjected to flash  
15 column chromatography over silica gel (230-400 mesh) using hexane as the  
16 eluent to afford the title compound (0.74g, 74%) as a clear oil.

17 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.34 (d, 1H, *J* = 2.3Hz), 7.23 (dd, 1H, *J* =  
18 2.3, 8.5Hz), 6.77 (d, 1H, *J* = 8.0Hz), 4.61 (d, 1H, *J* = 0.73Hz), 4.17 (d, 1H, *J* =  
19 0.73Hz), 2.33 (s, 2H), 1.27 (s, 6H).

20 GENERAL PROCEDURE Q: 6-Bromo-3,4-dihydro-4,4-dimethylspiro[2H-1-  
21 benzopyran-2,1'-cyclopropane] (**Intermediate 36**)

22 A solution of diethyl zinc in hexane (1M, 7.1mL) was treated with  
23 diiodomethane (1.89g, 7.1mmol). After 5 minutes, a solution of 6-bromo-4,4-  
24 dimethyl-2-methylene chroman (**Intermediate 35**, 0.44g, 1.77mmol) in 3mL  
25 of hexane was added and the solution was refluxed for 1h. The reaction  
26 mixture was then cooled to ambient temperature, diluted with hexane, washed  
27 with brine (x1), dried over anhydrous sodium sulfate, filtered and evaporated  
28 in *vacuo* to a residue which was subjected to flash column chromatography



1 over silica gel (230-400 mesh) using hexane as the eluent to obtain the title  
2 compound (0.44g, 93%).

3 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.47 (d, 1H, *J* = 2.3Hz), 7.23 (dd, 1H, *J* =  
4 2.3, 8.5Hz), 6.70 (d, 1H, *J* = 8.0Hz), 1.96 (s, 2H), 1.47 (s, 6H), 1.09-1.05 (m,  
5 2H), 0.74-0.70 (m, 2H).

6 3,4-Dihydro-4,4-dimethyl-6-(trimethylsilanyl)ethynylspiro[2H-1-benzopyran-  
7 2,1'-cyclopropane] (**Intermediate 37**)

8 Following general procedure D and using 6-bromo-3,4-dihydro-4,4-  
9 dimethylspiro[2H-1-benzopyran-2,1'-cyclopropane] (**Intermediate 36**, 0.44g,  
10 1.65mmol), triethyl amine (4mL), anhydrous tetrahydrofuran (5mL),  
11 copper(I)iodide (0.95g, 0.5mmol), trimethylsilyl acetylene (1.62g, 16.5mmol)  
12 and dichlorobis(triphenylphosphine)palladium(II) (0.4g, 0.56mmol), the title  
13 compound was obtained as a brown oil (0.4g, 86%).

14 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.44 (d, 1H, *J* = 2.1Hz), 7.18 (dd, 1H, *J* =  
15 2.1, 8.5Hz), 6.65 (d, 1H, *J* = 8.5Hz), 1.87 (s, 2H), 1.37 (s, 6H), 1.01-0.97 (m,  
16 2H), 0.65-0.61 (m, 2H), 0.26 (s, 9H).

17 6-Ethynyl-3,4-dihydro-4,4-dimethylspiro[2H-1-benzopyran-2,1'-  
18 cyclopropane] (**Intermediate 38**)

19 Following general procedure E and using 3,4-dihydro-4,4-dimethyl-6-  
20 (trimethylsilanyl)ethynylspiro[2H-1-benzopyran-2,1'-cyclopropane]  
21 (**Intermediate 37**, 0.4g, 1.42mmol), potassium carbonate (0.98g, 7.1mmol)  
22 and methanol, the title compound was obtained as a yellow oil (0.3g, 100%).

23 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.44 (d, 1H, *J* = 2.1Hz), 7.18 (dd, 1H, *J* = 2.1,  
24 8.5Hz), 6.65 (d, 1H, *J* = 8.5Hz), 2.97 (s, 1H), 1.86 (s, 2H), 1.37 (s, 6H), 1.00-  
25 0.95 (m, 2H), 0.64-0.59 (m, 2H).

26 Benzoic acid, 4-[(3,4-dihydro-4,4-dimethylspiro[2H-1-benzopyran-2,1'-  
27 cyclopropane]-6-yl)ethynyl]-ethyl ester (**Compound 39, General Formula 1**)

28 Following general procedure F and using 6-ethynyl-3,4-dihydro-4,4-  
29 dimethylspiro[2H-1-benzopyran-2,1'-cyclopropane] (**Intermediate 38**, 0.06g,

1 0.28mmol), ethyl-4-iodo-benzoate (**Reagent A**, 0.086g, 0.31mmol), triethyl  
2 amine (4mL), tetrahydrofuran(4mL), copper(I)iodide(0.032g, 0.17mmol) and  
3 dichlorobis(triphenylphosphine)palladium(II) (0.118g, 0.17mmol) followed by  
4 flash column chromatography over silica gel (230-400 mesh) using 5-10 %  
5 ethyl acetate in hexane as the eluent, the title compound was obtained (0.07g,  
6 70%).

7 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 8.01 (d, 2H, *J* = 8.2Hz), 7.56 (d, 2H, *J* =  
8 8.5Hz), 7.49 (d, 1H, *J* = 2.1Hz), 7.24 (dd, 1H, *J* = 2.1, 8.5Hz), 6.70 (d, 1H, *J* =  
9 8.5Hz), 4.38 (q, 2H, *J* = 7.1Hz), 1.89 (s, 2H), 1.40 (s, 6H), 1.40 (t, 3H, *J* =  
10 7.0Hz), 1.02-0.98 (m, 2H), 0.67-0.62 (m, 2H).

11 Benzoic acid, 4-[(3,4-dihydro-4,4-dimethylspiro[2*H*-1-benzopyran-2,1'-  
12 cyclopropane]-6-yl)ethynyl]- (**Compound 40, General Formula 1**)

13 Following general procedure L and using benzoic acid, 4-[(3,4-dihydro-4,4-  
14 dimethylspiro[2*H*-1-benzopyran-2,1'-cyclopropane]-6-yl)ethynyl]-ethyl ester  
15 (**Compound 39**, 0.07g, 0.196mmol), 5mL of ethanol and 1M sodium  
16 hydroxide solution (2mL) followed by preparative reverse phase HPLC using  
17 10% water in acetonitrile as the mobile phase, the title compound was  
18 obtained as a solid (0.034g, 52%).

19 <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>COCD<sub>3</sub>): δ 8.05 (d, 2H, *J* = 8.2Hz), 7.64 (d, 2H, *J* =  
20 8.2Hz), 7.60 (d, 1H, *J* = 2.1Hz), 7.28 (dd, 1H, *J* = 2.1, 8.5Hz), 6.73 (d, 1H, *J* =  
21 8.5Hz), 1.95 (s, 2H), 1.43 (s, 6H), 0.96-0.92 (m, 2H), 0.74-0.71 (m, 2H).

22 Benzeneacetic acid, 4-[(3,4-dihydro-4,4-dimethylspiro[2*H*-1-benzopyran-2,1'-  
23 cyclopropane]-6-yl)ethynyl]-methyl ester (**Compound 41, General Formula**  
24 **1**)

25 Following general procedure F and using 6-ethynyl-3,4-dihydro-4,4-  
26 dimethylspiro[2*H*-1-benzopyran-2,1'-cyclopropane] (**Intermediate 38**, ,  
27 0.060g, 0.28mmol), methyl-4-iodo phenyl acetate (**Reagent B**, 0.078g,  
28 0.28mmol), triethyl amine (4mL), tetrahydrofuran (4mL), copper(I)iodide  
29 (0.032g, 0.17mmol) and dichlorobis(triphenylphosphine)palladium(II)

(0.118g, 0.17mmol) followed by flash column chromatography over silica gel (230-400 mesh) using 5 % ethyl acetate in hexane as the eluent, the title compound was obtained (0.084g, 84%).

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.48-7.45 (m, 3H), 7.26-7.20 (m, 3H), 6.67 (d, 1H, *J* = 8.5Hz), 3.70 (s, 3H), 3.63 (s, 2H), 1.89 (s, 2H), 1.40 (s, 3H), 1.40 (s, 3H), 1.01-0.97 (m, 2H), 0.67-0.61 (m, 2H).

Benzeneacetic acid, 4-[(3,4-dihydro-4,4-dimethylspiro[2H-1-benzopyran-2,1'-cyclopropane]-6-yl)ethynyl]- (**Compound 42, Formula 1**)

A solution of benzeneacetic acid, 4-[(3,4-dihydro-4,4-dimethylspiro[2H-1-benzopyran-2,1'-cyclopropane]-6-yl)ethynyl]-methyl ester (**Compound 41**, 0.084g, 0.24mmol) in 5mL of methanol was treated with 1M sodium hydroxide solution (2mL) and heated at 55°C for 2h. The volatiles were distilled off in *vacuo* and the residue was acidified with 10% hydrochloric acid and extracted with ethyl acetate (x2). The combined organic phase was washed with brine (x1), dried over anhydrous sodium sulfate, filtered and evaporated in *vacuo* to a residue which was purified by preparative reverse phase HPLC using 10% water in acetonitrile as the mobile phase to afford the title compound (0.080g, 100%).

<sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>COCD<sub>3</sub>): δ 7.49-7.46 (m, 3H), 7.25 (d, 2H, *J* = 8.2Hz), 7.22 (dd, 1H *J* = 2.1, 8.5Hz), 6.68 (d, 1H, *J* = 8.5Hz), 3.66 (s, 2H), 1.88 (s, 2H), 1.44 (s, 6H), 1.01-0.97 (m, 2H), 0.67-0.61 (m, 2H).

2-Fluoro-benzoic acid, 4-[(3,4-dihydro-4,4-dimethylspiro[2H-1-benzopyran-2,1'-cyclopropane]-6-yl)ethynyl]-methyl ester (**Compound 43, General Formula 1**)

Following general procedure F and 6-ethynyl-3,4-dihydro-4,4-dimethylspiro[2H-1-benzopyran-2,1'-cyclopropane] (**Intermediate 38**, 0.050g, 0.23mmol), methyl-2-fluoro-4-iodo-benzoate (**Reagent G**, 0.069g, 0.24mmol), triethyl amine (5mL), tetrahydrofuran(5mL), copper(I)iodide(0.013g, 0.07mmol) and

1 dichlorobis(triphenylphosphine)palladium(II) (0.049g, 0.07mmol) followed by  
2 flash column chromatography over silica gel (230-400 mesh) using 5-10 %  
3 ethyl acetate in hexane as the eluent, the title compound was obtained (0.080g,  
4 100%).

5 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.90 (t, 1H, *J* = 7.9Hz), 7.63 (d, 1H, *J* =  
6 1.8Hz), 7.32 (dd, 1H, *J* = 1.5, 8.2Hz), 7.26 (dd, 1H, *J* = 1.5, 11.4Hz), 7.24 (dd,  
7 1H, *J* = 2.1, 8.5Hz), 6.71 (d, 1H, *J* = 8.5Hz), 1.97 (s, 2H), 1.44 (s, 6H), 0.98-  
8 0.94 (m, 2H), 0.76-0.71 (m, 2H).

9 2-Fluoro-benzoic acid, 4-[(3,4-dihydro-4,4-dimethylspiro[2H-1-benzopyran-  
10 2,1'-cyclopropane]-6-yl)ethynyl]- (Compound 44, General Formula 1)

11 Following general procedure L and using 2-fluoro-benzoic acid, 4-  
12 [(3,4-dihydro-4,4-dimethylspiro[2H-1-benzopyran-2,1'-cyclopropane]-6-  
13 yl)ethynyl]-methyl ester (Compound 43, 0.08g, 0.23mmol), 5mL of methanol  
14 and 2M sodium hydroxide solution (1mL) followed by flash column  
15 chromatography over silica gel (230-400 mesh) using ethyl acetate as the  
16 eluent, the title compound was obtained (0.020g, 25%).

17 <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>COCD<sub>3</sub>): δ 7.99 (t, 1H, *J* = 7.9Hz), 7.63 (d, 1H, *J* =  
18 2.1Hz), 7.44 (dd, 1H, *J* = 1.5, 7.9Hz), 7.37 (dd, 1H, *J* = 1.5, 11.4Hz), 7.31 (dd,  
19 1H, *J* = 2.1, 8.5Hz), 6.75 (d, 1H, *J* = 8.2Hz), 1.97 (s, 2H), 1.44 (s, 6H), 0.98-  
20 0.94 (m, 2H), 0.76-0.71 (m, 2H).

21 GENERAL PROCEDURE R: 2,2,4,4-Tetramethyl-chroman-6-carboxylic acid  
22 (Intermediate 39)

23 A stirred, cooled (-78°C) solution of 6-bromo-2,2,4,4-tetramethyl  
24 chroman (1.2g, 4.47mmol) in 15mL of anhydrous tetrahydrofuran was treated  
25 with a 1.7M solution of *tert*-butyl lithium solution in pentane ( 5.27mL,  
26 8.9mmol). After 10 minutes at -78°C, carbon dioxide (generated from dry ice)  
27 was bubbled into the reaction mixture. The reaction mixture was allowed to  
28 warm to ambient temperature. The reaction mixture was diluted with ethyl  
29 acetate, washed with brine, dried over anhydrous sodium sulfate, filtered and

1 evaporated in *vacuo* to a residue which was subjected to flash column  
2 chromatography over silica gel (230-400 mesh) using ethyl acetate as the  
3 eluent to afford the title compound as a white solid (1.1g, 92%).  
4 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 12.17 (br s, 1H), 8.09 (d, 1H, *J* = 2.1Hz), 7.85  
5 (dd, 1H, *J* = 2.1, 8.5Hz), 6.83 (d, 1H, *J* = 8.2Hz), 1.87 (s, 2H), 1.39 (s, 6H),  
6 1.37 (s, 6H).

7 2,2,4,4-Tetramethyl-chroman-6-carboxylic acid 4-(*tert*-  
8 butoxycarbonylmethyl)phenyl ester (Compound 45, General Formula 8)

9 A solution of 2,2,4,4-tetramethyl chroman-6-carboxylic acid (0.1g,  
10 0.43mmol) in thionyl chloride (10mL) was refluxed for 2h. The thionyl  
11 chloride was evaporated under reduced pressure and the residue was dissolved  
12 in 5mL of dichloromethane and treated with triethyl amine (5mL) followed by  
13 *tert*-butyl-4-hydroxy phenyl acetate (**Reagent E**, 0.088g, 0.427mmol). After  
14 0.5h, the reaction mixture was subjected to flash column chromatography over  
15 silica gel (230-400 mesh) using 5-10% ethyl acetate in hexane as the eluent to  
16 afford the title compound (0.1g, 55%).

17 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 8.15 (d, 1H, *J* = 2.1Hz), 7.93 (dd, 1H, *J* = 2.1,  
18 8.5Hz), 7.33 (d, 2H, *J* = 8.8Hz), 7.16 (d, 2H, *J* = 8.8Hz), 6.88 (d, 1H, *J* =  
19 8.5Hz), 3.54 (s, 2H), 1.89 (s, 2H), 1.45 (s, 9H), 1.41 (s, 6H), 1.40 (s, 6H).

20 2,2,4,4-Tetramethyl-chroman-6-carboxylic acid 4-(carboxymethyl)phenyl  
21 ester (Compound 46, General Formula 8)

22 A solution of 2,2,4,4-tetramethyl-chroman-6-carboxylic acid 4-(*tert*-  
23 butoxycarbonylmethyl)phenyl ester (**Compound 45**, 0.1g, 0.23mmol) was  
24 treated with 5mL of trifluoroacetic acid and stirred at ambient temperature for  
25 1h. The trifluoroacetic acid was distilled off under reduced pressure and the  
26 residue was subjected to preparative reverse phase HPLC using 10% water in  
27 acetonitrile as the mobile phase to afford the title compound as a white solid  
28 (0.045g, 50%).

1 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 8.13 (d, 1H, *J* = 2.1Hz), 7.92 (dd, 1H, *J* = 2.3,  
2 8.5Hz), 7.35 (d, 2H, *J* = 8.8Hz), 7.17 (d, 2H, *J* = 8.5Hz), 6.87 (d, 1H, *J* =  
3 8.5Hz), 3.68 (s, 2H), 1.89 (s, 2H), 1.41 (s, 6H), 1.39 (s, 6H).

4 6-Bromo-8-carbaldehyde-3,4-dihydro-4,4-dimethylspiro[2H-1-benzopyran-  
5 2,1'-cyclopropane] (**Intermediate 40**)

6 Following general procedure M and using 6-bromo-3,4-dihydro-4,4-  
7 dimethylspiro[2H-1-benzopyran-2,1'-cyclopropane](**Intermediate 36**, 2.3g,  
8 8.65mmol), anhydrous dichloromethane (25mL), 1M solution (8.65mL,  
9 8.65mmol) of titanium tetrachloride in dichloromethane and α,α-dichloro  
10 methyl ether (1.09g, 9.52mmol) followed by flash column chromatography  
11 using 10% ethyl acetate in hexane as the eluent, the title compound was  
12 obtained as a yellow solid (2.06g, 81%).

13 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 10.20 (s, 1H), 7.69 (d, 1H, *J* = 2.6Hz), 7.58 (d,  
14 1H, *J* = 2.6Hz), 1.92 (s, 2H), 1.40 (s, 6H), 1.09-1.04 (m, 2H), 0.73-0.69 (m,  
15 2H).

16 6-Bromo-3,4-dihydro-4,4-dimethyl-8-vinylspiro[2H-1-benzopyran-2,1'-  
17 cyclopropane] (**Intermediate 41**)

18 Following general procedure N and using A solution of methyldiene  
19 triphenyl phosphorane [generated from methyl triphenylphosphonium bromide  
20 (7g, 20mmol) and 1.6M solution of *n*-butyl lithium in hexanes (11.8mL,  
21 19mmol)], 6-bromo-8-carbonyl-3,4-dihydro-4,4-dimethylspiro[2H-1-  
22 benzopyran-2,1'-cyclopropane](**Intermediate 40**, 2.06g, 7mmol) followed by  
23 flash column chromatography over silica gel (230-400 mesh) using 1-2% ethyl  
24 acetate in hexane as the eluent, the title compound was obtained as a clear oil  
25 (1.36g, 66%).

26 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.36 (d, 1H, *J* = 2.3Hz), 7.28 (d, 1H, *J* =  
27 2.6Hz), 6.80 (dd, 1H, *J* = 11.1, 17.9Hz), 5.63 (dd, 1H, *J* = 1.2, 17.9Hz), 5.19  
28 (dd, 1H, *J* = 1.2, 11.1Hz), 1.84 (s, 2H), 1.35 (s, 6H), 0.97 (t, 2H, *J* = 6.3Hz),  
29 0.62 (d, 1H, *J* = 5.3Hz), 0.60 (d, 1H, *J* = 6.2Hz).

1 6-Bromo-8-cyclopropyl-3,4-dihydro-4,4-dimethylspiro[2H-1-benzopyran-  
2 2,1'-cyclopropane] (**Intermediate 42**)

3       Following general procedure O and using A 6-bromo-3,4-dihydro-4,4-  
4 dimethyl-8-vinylspiro[2H-1-benzopyran-2,1'-cyclopropane] (**Intermediate**  
5 **41**, 1.36g, 4.6mmol), a solution of diazomethane in diethyl ether and  
6 palladium (II)acetate (~30mg) followed by flash column chromatography over  
7 silica gel (230-400 mesh) using hexane as the eluent, the title compound was  
8 obtained as a clear oil (1.38g, 100%).

9 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.19 (d, 1H, *J* = 2.2Hz), 6.71 (d, 1H, *J* =  
10 2.2Hz), 1.99-1.92 (m, 1H), 1.87 (s, 2H), 1.35 (s, 6H), 1.00-0.95 (m, 2H), 0.90-  
11 0.82 (m, 2H), 0.65-0.54 (m, 4H).

12 8-Cyclopropyl-3,4-dihydro-4,4-dimethyl-6-(trimethylsilyl)ethynylspiro[2H-  
13 1-benzopyran-2,1'-cyclopropane] (**Intermediate 43**)

14       Following general procedure D and 6-bromo-8-cyclopropyl-3,4-  
15 dihydro-4,4-dimethylspiro[2H-1-benzopyran-2,1'-cyclopropane]  
16 (**Intermediate 42**, 0.74g, 2.4mmol), (trimethylsilyl)acetylene (4mL, 28mmol),  
17 triethyl amine (8mL), anhydrous tetrahydrofuran, copper(I)iodide (0.050g,  
18 0.26mmol) and dichlorobis(triphenylphosphine)palladium(II) (0.15g,  
19 0.22mmol), followed by flash column chromatography over silica gel (230-  
20 400 mesh) using 1-2% ethyl acetate in hexane as the eluent, the title compound  
21 was obtained as an oil (0.62g, 80%).

22 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.28 (d, 1H, *J* = 1.9Hz), 6.77 (d, 1H, *J* =  
23 1.9Hz), 2.03-1.94 (m, 1H), 1.91 (s, 2H), 1.40 (s, 6H), 1.05-0.98 (m, 2H), 0.95-  
24 0.83 (m, 2H), 0.69-0.59 (m, 4H), 0.27 (s, 9H).

25 8-Cyclopropyl-6-ethynyl-3,4-dihydro-4,4-dimethylspiro[2H-1-benzopyran-  
26 2,1'-cyclopropane] (**Intermediate 44**)

27       Following general procedure E, and 8-cyclopropyl-3,4-dihydro-4,4-  
28 dimethyl-6-(trimethylsilyl)ethynylspiro[2H-1-benzopyran-2,1'-  
29 cyclopropane] (**Intermediate 43**, 0.62g, 1.9mmol), methanol and potassium

1 carbonate (0.5g, 3.6mmol) followed by flash column chromatography over  
2 silica gel (230-400 mesh) using 1-2% ethyl acetate in hexane as the eluent, the  
3 title compound was obtained as an oil (0.5g, 100%).

4 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.30 (d, 1H, *J* = 1.8Hz), 6.80 (d, 1H, *J* =  
5 2.0Hz), 2.97 (s, 1H), 2.04-1.95 (m, 1H), 1.91 (s, 2H), 1.39 (s, 6H), 1.20-0.90  
6 (m, 2H), 0.90-0.84 (m, 2H), 0.75-0.58 (m, 4H).

7 Benzeneacetic acid, 4-[(8-cyclopropyl-3,4-dihydro-4,4-dimethylspiro[2H-1-  
8 benzopyran-2,1'-cyclopropane]-6-yl)ethynyl]-methyl ester (Compound 47,  
9 **General Formula 1)**

10 Following general procedure F and using 8-cyclopropyl-6-ethynyl-3,4-  
11 dihydro-4,4-dimethylspiro[2H-1-benzopyran-2,1'-cyclopropane]  
12 (**Intermediate 44**, 0.11g, 0.43mmol), methyl-4-iodo phenyl acetate (**Reagent**  
13 **B**, 0.114g, 0.41mmol), triethyl amine (5mL), tetrahydrofuran (3mL),  
14 copper(I)iodide (0.025g, 0.13mmol) and  
15 dichlorobis(triphenylphosphine)palladium(II) (0.075g, 0.11mmol), the title  
16 compound was obtained as a clear oil (0.096g, 56%).

17 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.46 (d, 2H, *J* = 8.0Hz), 7.31 (d, 1H, *J* =  
18 1.9Hz), 7.24 (d, 2H, *J* = 8.2Hz), 6.81 (d, 1H, *J* = 1.9Hz), 3.69 (s, 3H), 3.62 (s,  
19 2H), 2.04-1.95 (m, 1H), 1.90 (s, 2H), 1.39 (s, 6H), 1.03-0.99 (m, 2H), 0.90-  
20 0.83 (m, 2H), 0.68-0.59 (m, 4H).

21 Benzeneacetic acid, 4-[(8-cyclopropyl-3,4-dihydro-4,4-dimethylspiro[2H-1-  
22 benzopyran-2,1'-cyclopropane]-6-yl)ethynyl]- (Compound 48, General  
23 **Formula 1)**

24 Following general procedure L and using benzeneacetic acid, 4-[(8-  
25 cyclopropyl-3,4-dihydro-4,4-dimethylspiro[2H-1-benzopyran-2,1'-  
26 cyclopropane]-6-yl)ethynyl]-methyl ester (**Compound 47**, 0.96g, 0.24mmol),  
27 5mL of methanol and 1M sodium hydroxide solution (2mL) followed by flash  
28 column chromatography over silica gel (230-400 mesh) using 15% methanol



1 in dichloromethane as the eluent, the title compound was obtained as a solid  
2 (0.084g, 91%).  
3 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 10.27 (br s, 1H), 7.46 (d, 2H, *J* = 8.2Hz), 7.30  
4 (d, 1H, *J* = 1.8Hz), 7.23 (d, 2H, *J* = 8.2Hz), 6.80 (d, 1H, *J* = 1.5Hz), 3.63 (s,  
5 2H), 2.07-1.94 (m, 1H), 1.89 (s, 2H), 1.39 (s, 6H), 1.03-0.98 (m, 2H), 0.89-  
6 0.82 (m, 2H), 0.73-0.59 (m, 4H).

7 4-[(8-Cyclopropyl-3,4-dihydro-4,4-dimethylspiro[2H-1-benzopyran-2,1'-  
8 cyclopropane]-6-yl)ethynyl]-2-fluoro-benzeneacetic acid methyl ester  
9 **(Compound 49, General Formula 1)**

10 Following general procedure F and using 8-cyclopropyl-6-ethynyl-3,4-  
11 dihydro-4,4-dimethylspiro[2H-1-benzopyran-2,1'-cyclopropane]  
12 **(Intermediate 44, 0.125g, 0.5mmol)**, methyl-2-fluoro-4-iodo phenyl acetate  
13 **(Reagent H, 0.14g, 0.5mmol)**, triethyl amine (3mL), tetrahydrofuran (3mL),  
14 copper(I)iodide (0.020g, 0.1mmol) and  
15 dichlorobis(triphenylphosphine)palladium(II) (0.060g, 0.085mmol) followed  
16 by preparative normal phase HPLC using 10% ethyl acetate in hexane as the  
17 mobile phase, the title compound was obtained (0.096g, 46%).

18 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.30 (d, 1H, *J* = 2.1Hz), 7.26-7.18 (m, 3H),  
19 6.80 (d, 1H, *J* = 1.8Hz), 3.71 (s, 3H), 3.67 (s, 2H), 2.04-1.94 (m, 1H), 1.90 (s,  
20 2H), 1.40 (s, 6H), 1.18-0.99 (m, 2H), 0.90-0.83 (m, 2H), 0.68-0.59 (m, 4H).

21 4-[(8-Cyclopropyl-3,4-dihydro-4,4-dimethylspiro[2H-1-benzopyran-2,1'-  
22 cyclopropane]-6-yl)ethynyl]-2-fluoro-benzeneacetic acid **(Compound 50,**  
23 **General Formula 1)**

24 Following general procedure L and using 4-[(8-cyclopropyl-3,4-  
25 dihydro-4,4-dimethylspiro[2H-1-benzopyran-2,1'-cyclopropane]-6-  
26 yl)ethynyl]-2-fluoro-benzeneacetic acid methyl ester **(Compound 49, 0.096g,**  
27 **0.23mmol)**, 5mL of methanol and 1M sodium hydroxide solution (2mL)  
28 followed by flash column chromatography over silica gel (230-400 mesh)

1 using 15% methanol in dichloromethane as the eluent, the title compound was  
2 obtained as a solid (0.093g, 100%).

3 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 9.50 (br s, 1H), 7.27 (d, 1H, *J* = 2.1Hz), 7.24-  
4 7.15 (m, 3H), 6.77 (d, 1H, *J* = 1.5Hz), 3.67 (s, 2H), 2.01-1.91 (m, 1H), 1.87 (s,  
5 2H), 1.36 (s, 6H), 1.01-0.96 (m, 2H), 0.87-0.80 (m, 2H), 0.65-0.56 (m, 4H).

6 Benzoic acid, 4-[(8-cyclopropyl-3,4-dihydro-4,4-dimethylspiro[2H-1-  
7 benzopyran-2,1'-cyclopropane]-6-yl)ethynyl]-ethyl ester (Compound 51,  
8 **General Formula 1**)

9 Following general procedure F and using 8-cyclopropyl-6-ethynyl-3,4-  
10 dihydro-4,4-dimethylspiro[2H-1-benzopyran-2,1'-cyclopropane]  
11 (Intermediate 44, 0.05g, 0.2mmol), ethyl-4-iodo-benzoate (Reagent A,  
12 0.055g, 0.2mmol), triethyl amine (3mL), tetrahydrofuran(3mL),  
13 copper(I)iodide(0.020g, 0.1mmol) and  
14 dichlorobis(triphenylphosphine)palladium(II) (0.060g, 0.085mmol), the title  
15 compound was obtained (0.06g, 75%).

16 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 8.00 (d, 2H, *J* = 8.2Hz), 7.55 (d, 2H, *J* =  
17 8.2Hz), 7.33 (d, 1H, *J* = 1.8Hz), 6.83 (d, 1H, *J* = 2.1Hz), 4.38 (q, 2H, *J* =  
18 7.1Hz), 2.04-1.95 (m, 1H), 1.91 (s, 2H), 1.40 (s, 6H), 1.40 (t, 3H, *J* = 7.0Hz),  
19 1.05-0.95 (m, 2H), 0.91-0.84 (m, 2H), 0.69-0.61 (m, 4H).

20 Benzoic acid, 4-[(8-cyclopropyl-3,4-dihydro-4,4-dimethylspiro[2H-1-  
21 benzopyran-2,1'-cyclopropane]-6-yl)ethynyl]- (Compound 52, General  
22 **Formula 1**)

23 Following general procedure L and using benzoic acid, 4-[(8-  
24 cyclopropyl-3,4-dihydro-4,4-dimethylspiro[2H-1-benzopyran-2,1'-  
25 cyclopropane]-6-yl)ethynyl]-ethyl ester (Compound 51, 0.06g, 0.15mmol),  
26 5mL of methanol and 1M sodium hydroxide solution (2mL) followed by  
27 preparative reverse phase HPLC using 10% water in acetonitrile as the mobile  
28 phase, the title compound was obtained as a solid (0.040g, 72%).

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 8.08 (d, 2H, *J* = 8.8Hz), 7.60 (d, 2H, *J* = 8.8Hz), 7.34 (d, 1H, *J* = 1.9Hz), 6.84 (d, 1H, *J* = 1.9Hz), 2.05-1.96 (m, 1H), 1.92 (s, 2H), 1.41 (s, 6H), 1.05-0.95 (m, 2H), 0.92-0.83 (m, 2H), 0.75-0.60 (m, 4H).

4-[(8-Cyclopropyl-3,4-dihydro-4,4-dimethylspiro[2*H*-1-benzopyran-2,1'-cyclopropane]-6-yl)ethynyl]-2-fluoro-benzoic acid methyl ester (Compound 53, General Formula 1)

Following general procedure F and using 8-cyclopropyl-6-ethynyl-3,4-dihydro-4,4-dimethylspiro[2*H*-1-benzopyran-2,1'-cyclopropane] (Intermediate 44, 0.03g, 0.11mmol), methyl-2-fluoro-4-iodo-benzoate (Reagent G, 0.025g, 0.09mmol), triethyl amine (3mL), tetrahydrofuran(3mL), copper(I)iodide(0.020g, 0.1mmol) and dichlorobis(triphenylphosphine)palladium(II) (0.06g, 0.085mmol) followed by preparative normal phase HPLC using 10% ethyl acetate in hexane as the mobile phase, the title compound was obtained as a white solid (0.019g, 40%).  
<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.97 (t, 1H, *J* = 7.8Hz), 7.34 (d, 1H, *J* = 1.9Hz), 7.32-7.25 (m, 2H), 6.83 (d, 1H, *J* = 1.9Hz), 3.95 (s, 3H), 2.06-1.96 (m, 1H), 1.93 (s, 2H), 1.42 (s, 6H), 1.06-1.02 (m, 2H), 0.91-0.86 (m, 2H), 0.71-0.61 (m, 4H).

4-[(8-Cyclopropyl-3,4-dihydro-4,4-dimethylspiro[2*H*-1-benzopyran-2,1'-cyclopropane]-6-yl)ethynyl]-2-fluoro-benzoic acid (Compound 54, General Formula 1)

Following general procedure L and using 4-[(8-cyclopropyl-3,4-dihydro-4,4-dimethylspiro[2*H*-1-benzopyran-2,1'-cyclopropane]-6-yl)ethynyl]-2-fluoro-benzoic acid methyl ester (Compound 53, 0.019g, 0.047mmol), 5mL of methanol and 1M sodium hydroxide solution (2mL) followed by preparative reverse phase HPLC using 10% water in acetonitrile as the mobile phase, the title compound was obtained as a solid (0.01g, 56%).

1 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.99 (t, 1H, *J* = 8.0Hz), 7.36 -7.28 (m, 3H),  
2 6.83 (d, 1H, *J* = 1.9Hz), 2.18-1.95 (m, 1H), 1.92 (s, 2H), 1.41 (s, 6H), 1.06-  
3 1.01 (m, 2H), 0.96-0.83 (m, 2H), 0.76-0.60 (m, 4H).

4 8-Acetyl-6-bromo-2,2,4,4-tetramethyl chroman (Intermediate 45)

5 A stirred, cooled (ice bath) suspension of aluminum chloride (0.99g,  
6 7.46mmol) in anhydrous dichloromethane (20 mL) was treated with acetyl  
7 chloride (0.58g, 7.46mmol). After 5 minutes, a solution of 6-bromo-2,2,4,4-  
8 tetramethyl chroman (1g, 3.73mmol) in dichloromethane was added. The  
9 reaction was allowed to warm to ambient temperature and stirred for 2h. The  
10 reaction mixture was then poured into ice containing 10% hydrochloric acid  
11 and extracted with diethyl ether (x2). The combined organic phase was  
12 washed with saturated aqueous sodium bicarbonate solution, dried over  
13 anhydrous sodium sulfate, filtered and evaporated in *vacuo* to a residue which  
14 was subjected to flash column chromatography over silica gel (230-400 mesh)  
15 using 5% ethyl acetate in hexane as the eluent to afford the title compound as a  
16 pale yellow oil (0.95g, 83%). It was used as such for the next step without any  
17 characterization.

18 6-Bromo-8-ethyl-2,2,4,4-tetramethyl chroman (Intermediate 46)

19 A stirred, cooled (ice bath) solution of 8-acetyl-6-bromo-2,2,4,4-  
20 tetramethyl chroman (Intermediate 45, 0.95g, 3.1mmol) in trifluoroacetic  
21 acid (10mL) was treated with triethylsilane (10mL) and the resulting reaction  
22 mixture was allowed to warm to ambient temperature and stirred overnight.  
23 The volatiles were distilled off in *vacuo* and the residue was diluted with water  
24 and extracted with hexane (x2). The combined organic phase was dried over  
25 anhydrous sodium sulfate, filtered and evaporated in *vacuo* to an oil which  
26 was subjected to flash column chromatography over silica gel (230-400 mesh)  
27 using hexane as the eluent to afford the title compound as a clear oil,  
28 contaminated with a small amount of triethylsilane (0.51g, 56%).

1 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.23 (d, 1H, *J* = 2.3Hz), 7.08 (d, 1H, *J* =  
2 2.3Hz), 2.58 (q, 2H, *J* = 7.6Hz), 1.81 (s, 2H), 1.34 (s, 6H), 1.33 (s, 6H), 1.17  
3 (t, 3H, *J* = 7.6Hz).  
4 8-Ethyl-6-trimethylsilanylethynyl-2,2,4,4-tetramethyl chroman (**Intermediate**  
5 **47**)

6 Following general procedure D and using 6-bromo-8-ethyl-2,2,4,4-  
7 tetramethyl chroman (**Intermediate 46**, 0.5g, 1.61mmol),  
8 (trimethylsilyl)acetylene (1.57g, 16.1mmol), triethyl amine (8mL), anhydrous  
9 tetrahydrofuran (10mL), copper(I)iodide (0.025g, 0.13mmol) and  
10 dichlorobis(triphenylphosphine)palladium(II) (0.075g, 0.11mmol), followed  
11 by flash column chromatography over silica gel (230-400 mesh) using 5%  
12 ethyl acetate in hexane as the eluent, the title compound was obtained as an oil  
13 (0.137g, 27%).

14 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.27 (d, 1H, *J* = 2.1Hz), 7.10 (d, 1H, *J* =  
15 2.1Hz), 2.55 (q, 2H, *J* = 7.6Hz), 1.81 (s, 2H), 1.33 (s, 6H), 1.32 (s, 6H), 1.15  
16 (t, 3H, *J* = 7.6Hz), 0.24 (s, 9H).

17 8-Ethyl-6-ethynyl-2,2,4,4-tetramethyl chroman (**Intermediate 48**)

18 Following general procedure E and using 8-ethyl-6-  
19 trimethylsilanylethynyl-2,2,4,4-tetramethyl chroman (**Intermediate 47**,  
20 0.137g, 0.44mmol), methanol and potassium carbonate (0.1g, 0.72mmol)  
21 followed by flash column chromatography over silica gel (230-400 mesh)  
22 using 5% ethyl acetate in hexane as the eluent, the title compound was  
23 obtained as an oil (0.066g, 62%).

24 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.33 (d, 1H, *J* = 2.2Hz), 7.15 (d, 1H, *J* =  
25 1.6Hz), 2.99 (s, 1H), 2.59 (q, 2H, *J* = 7.6Hz), 1.84 (s, 2H), 1.37 (s, 6H), 1.35  
26 (s, 6H), 1.19 (t, 3H, *J* = 7.6Hz).

27 [4-(8-Ethyl-2,2,4,4-tetramethyl-chroman-6-yl-ethynyl) phenyl] acetic acid  
28 methyl ester (**Compound 55, General Formula 8**)

1       Following general procedure F and using 8-ethyl-6-ethynyl-2,2,4,4-  
2 tetramethylchroman (**Intermediate 48**, 0.033g, 0.136mmol), methyl-4-iodo  
3 phenyl acetate (**Reagent B**, 0.034g, 0.12mmol), triethyl amine (2mL),  
4 tetrahydrofuran (2mL), copper(I)iodide (0.025g, 0.13mmol) and  
5 dichlorobis(triphenylphosphine)palladium(II) (0.075g, 0.11mmol) the title  
6 compound was obtained (0.035g, 73%).  
7 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.49 (d, 2H, *J* = 7.9Hz), 7.35 (d, 1H, *J* =  
8 1.8Hz), 7.26 (d, 2H, *J* = 7.9Hz), 7.18 (d, 1H, *J* = 1.9Hz), 3.72 (s, 3H), 3.65 (s,  
9 2H), 2.61 (q, 2H, *J* = 7.5Hz), 1.85 (s, 2H), 1.38 (s, 12H), 1.21 (t, 3H, *J* =  
10 7.5Hz).

11 [4-(8-Ethyl-2,2,4,4-tetramethyl-chroman-6-yl-ethynyl) phenyl] acetic acid  
12 (**Compound 56, General Formula 8**)

13       Following general procedure L and using [4-(8-ethyl-2,2,4,4-  
14 tetramethyl-chroman-6-ylethynyl) phenyl] acetic acid methyl ester  
15 (**Compound 55**, 0.035g, 0.1mmol), 5mL of methanol and 1M sodium  
16 hydroxide solution (1mL) followed by preparative reverse phase HPLC using  
17 10% water in acetonitrile as the mobile phase, the title compound was  
18 obtained as a solid (0.11g, 25%).

19 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.48 (d, 2H, *J* = 8.0Hz), 7.33 (d, 1H, *J* =  
20 1.9Hz), 7.25 (d, 2H, *J* = 8.0Hz), 7.15 (d, 1H, *J* = 1.9Hz), 3.65 (s, 2H), 2.59 (q,  
21 2H, *J* = 7.5Hz), 1.83 (s, 2H), 1.35 (s, 12H), 1.18 (t, 3H, *J* = 7.4Hz).

22 Spiro[2H-1-benzopyran-2,1'-cyclopropane]-6-carboxylic acid, 8-cyclopropyl-  
23 3,4-dihydro-4,4-dimethyl- (**Intermediate 49**)

24       Following general procedure R and using 6-bromo-8-cyclopropyl-3,4-  
25 dihydro-4,4-dimethylspiro[2H-1-benzopyran-2,1'-cyclopropane]  
26 (**Intermediate 42**, 0.45g, 1.48mmol), anhydrous tetrahydrofuran (5mL), 1.7M  
27 solution of *tert*-butyl lithium solution in pentane ( 1.74mL, 2.96mmol) and  
28 carbon dioxide generated from dry ice, followed by flash column  
29 chromatography over silica gel (230-400 mesh) using 50% ethyl acetate in

1 hexane as the eluent, the title compound was obtained as a white solid (0.34g,  
2 85%).

3 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 12.43 (br s, 1H), 7.94 (d, 1H, *J* = 2.1Hz), 7.42  
4 (d, 1H, *J* = 1.8Hz), 2.06-1.96 (m, 1H), 1.92 (s, 2H), 1.42 (s, 6H), 1.12-0.97 (m,  
5 2H), 0.95-0.81 (m, 2H), 0.77-0.60 (m, 4H).

6 Spiro[2*H*-1-benzopyran-2,1'-cyclopropane]-6-carboxylic acid, 8-cyclopropyl-  
7 3,4-dihydro-4,4-dimethyl-, 4-(*tert*-butoxycarbonylmethyl)phenyl ester  
8 **(Compound 57, General Formula 1)**

9 A solution of spiro[2*H*-1-benzopyran-2,1'-cyclopropane]-6-carboxylic  
10 acid, 8-cyclopropyl-3,4-dihydro-4,4-dimethyl- (**Intermediate 49**, 0.06g,  
11 0.22mmol) in anhydrous dichloromethane (5mL) was treated with *tert*-butyl-4-  
12 hydroxy phenyl acetate (**Reagent E**, 0.05g, 0.22mmol) followed by 1-(3-  
13 dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.11g, 0.22mmol)  
14 and 4-dimethylaminopyridine (0.028g, 0.22mmol). The resulting solution was  
15 stirred at ambient temperature overnight. The reaction mixture was subjected  
16 to flash column chromatography over silica gel (230-400 mesh) using 7%  
17 ethyl acetate in hexane as the eluent to afford the title compound as a clear oil  
18 that solidified on standing (0.048g, 48%).

19 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.91 (d, 1H, *J* = 2.1Hz), 7.41 (d, 1H, *J* =  
20 1.8Hz), 7.24 (d, 2H, *J* = 8.8Hz), 7.05 (d, 2H, *J* = 8.5Hz), 3.46 (s, 2H), 1.97-  
21 1.90 (m, 1H), 1.87 (s, 2H), 1.37 (s, 9H), 1.36 (s, 6H), 1.04-0.90 (m, 2H), 0.87-  
22 0.75 (m, 2H), 0.65-0.56 (m, 4H).

23 Spiro[2*H*-1-benzopyran-2,1'-cyclopropane]-6-carboxylic acid, 8-cyclopropyl-  
24 3,4-dihydro-4,4-dimethyl-, 4-(carboxymethyl)phenyl ester (**Compound 58**,  
25 **General Formula 1**)

26 A solution of spiro[2*H*-1-benzopyran-2,1'-cyclopropane]-6-carboxylic  
27 acid, 8-cyclopropyl-3,4-dihydro-4,4-dimethyl-, 4-(*tert*-  
28 butoxycarbonylmethyl)phenyl ester (**Compound 57**, 0.048g, 0.105mmol) was  
29 treated with 2mL of trifluoroacetic acid and stirred at ambient temperature for

1 2h. The trifluoroacetic acid was distilled off under reduced pressure and the  
2 residue was subjected to preparative reverse phase HPLC using 10% water in  
3 acetonitrile as the mobile phase to afford the title compound as a white solid  
4 (0.029g, 55%).

5 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.99 (d, 1H, *J* = 2.2Hz), 7.48 (d, 1H, *J* =  
6 1.9Hz), 7.34 (d, 2H, *J* = 8.5Hz), 7.16 (d, 2H, *J* = 8.5Hz), 3.67 (s, 2H), 2.07-  
7 1.97 (m, 1H), 1.95 (s, 2H), 1.44 (s, 6H), 1.09-1.04 (m, 2H), 0.93-0.85 (m, 2H),  
8 0.79-0.64 (m, 4H).

9 Spiro[2*H*-1-benzopyran-2,1'-cyclopropane]-6-carboxylic acid, 8-cyclopropyl-  
10 3,4-dihydro-4,4-dimethyl-, 3-(*tert*-butoxycarbonylmethyl)phenyl ester  
11 **(Compound 59, General Formula 1)**

12 A solution of spiro[2*H*-1-benzopyran-2,1'-cyclopropane]-6-carboxylic  
13 acid, 8-cyclopropyl-3,4-dihydro-4,4-dimethyl- (**Intermediate 49**, 0.05g,  
14 0.18mmol) in anhydrous dichloromethane (5mL) was treated with *tert*-butyl-3-  
15 hydroxy phenyl acetate (**Reagent F**, 0.04g, 0.18mmol) followed by 1-(3-  
16 dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.029g, 0.1mmol)  
17 and 4-dimethylaminopyridine (0.022g, 0.18mmol). The resulting solution was  
18 stirred at ambient temperature overnight. The reaction mixture was subjected  
19 to flash column chromatography over silica gel (230-400 mesh) using 7%  
20 ethyl acetate in hexane as the eluent to afford the title compound as a clear oil  
21 that solidified on standing (0.020g, 23%).

22 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.98 (d, 1H, *J* = 1.9Hz), 7.48 (d, 1H, *J* =  
23 2.2Hz), 7.38 (t, 1H, *J* = 7.7Hz), 7.19-7.11 (m, 3H), 3.68 (s, 2H), 2.05-1.94 (m,  
24 1H), 1.95 (s, 2H), 1.44 (s, 15H), 1.09-1.04 (m, 2H), 0.96-0.82 (m, 2H), 0.73-  
25 0.64 (m, 4H).

26 Spiro[2*H*-1-benzopyran-2,1'-cyclopropane]-6-carboxylic acid, 8-cyclopropyl-  
27 3,4-dihydro-4,4-dimethyl-, 3-(carboxymethyl)phenyl ester (**Compound 60**,  
28 **General Formula 1**)



1       A solution of spiro[2*H*-1-benzopyran-2,1'-cyclopropane]-6-carboxylic  
2 acid, 8-cyclopropyl-3,4-dihydro-4,4-dimethyl-, 3-(*tert*-  
3 butoxycarbonylmethyl)phenyl ester (**Compound 59**, 0.020g, 0.04mmol) was  
4 treated with 2mL of trifluoroacetic acid and stirred at ambient temperature for  
5 2h. The trifluoroacetic acid was distilled off under reduced pressure and the  
6 residue was subjected to preparative reverse phase HPLC using 10% water in  
7 acetonitrile as the mobile phase to afford the title compound as a white solid  
8 (0.0125g, 62%).

9 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.99 (d, 1H, *J* = 2.1Hz), 7.49 (d, 1H, *J* =  
10 2.1Hz), 7.36 (t, 1H, *J* = 7.8Hz), 7.18-7.08 (m, 3H), 3.56 (s, 2H), 2.06-1.95 (m,  
11 1H), 1.95 (s, 2H), 1.45 (s, 6H), 1.09-1.05 (m, 2H), 0.96-0.84 (m, 2H), 0.74-  
12 0.65 (m, 4H).

13 6-Bromo-4,4-dimethyl-1,2,3,4-tetrahydro-quinoline-1-carbaldehyde  
14 (**Intermediate 50**)

15       A solution of 6-bromo-4,4-dimethyl-1,2,3,4-tetrahydroquinoline,  
16 available in accordance with United States Patent No. 5,089,509, the  
17 specification of which is incorporated herein by reference (1.8g, 7.5mmol) in  
18 10mL of formic acid was refluxed for 3h. The reaction mixture was then  
19 cooled to ambient temperature and poured into ice-cold saturated aqueous  
20 sodium bicarbonate solution and extracted with diethyl ether (x2). The  
21 combined organic phase was dried over anhydrous sodium sulfate, filtered and  
22 evaporated in *vacuo* to a residue which was subjected to flash column  
23 chromatography over silica gel (230-400 mesh) using 15-25% ethyl acetate in  
24 hexane as the eluent to afford the title compound as a pale yellow solid (1.8g,  
25 90%).

26 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 8.71 (s, 1H), 7.45 (d, 1H, *J* = 2.2Hz), 7.28 (dd,  
27 1H, *J* = 2.2, 8.5Hz), 6.98 (d, 1H, *J* = 8.5Hz), 3.78 (t, 2H, *J* = 6.3Hz), 1.74 (t,  
28 2H, *J* = 6.3Hz), 1.28 (s, 6H).

1 6-Bromo-1-cyclopropyl-4,4-dimethyl-1,2,3,4-tetrahydroquinoline

2 **(Intermediate 51)**

3 A stirred, cooled (0°C) solution of 6-bromo-4,4-dimethyl-1,2,3,4-  
4 tetrahydro-quinoline-1-carbaldehyde (**Intermediate 50**, 21.8, 6.7mmol) in  
5 anhydrous tetrahydrofuran (20mL) under argon was treated with titanium  
6 tetra-*iso*-propoxide (2.15mL, 7.39mmol) followed by 3M solution of ethyl  
7 magnesium bromide in diethyl ether (5.6mL, 16.8mmol) and the reaction  
8 mixture was then heated at 50°C overnight. It was then cooled in an ice-bath,  
9 quenched with saturated aqueous ammonium chloride solution and extracted  
10 with diethyl ether (x2). The combined organic phase was dried over anhydrous  
11 sodium sulfate, filtered over celite and evaporated in *vacuo* to residue which  
12 was subjected to flash column chromatography over silica gel (230-400 mesh)  
13 using 5% ethyl acetate in hexane as the eluent to afford the title compound as  
14 an oil (1.2g, 64%).

15 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.24 (d, 1H, *J* = 2.5Hz), 7.12 (dd, 1H, *J* = 2.2,  
16 8.8Hz), 7.01 (d, 1H, *J* = 8.8Hz), 3.20 (t, 2H, *J* = 6.0Hz), 2.27-2.20 (m, 1H),  
17 1.68 (t, 2H, *J* = 5.9Hz), 1.24 (s, 3H), 1.23 (s, 3H), 0.83-0.77 (m, 2H), 0.60-  
18 0.55 (m, 2H).

19 1-Cyclopropyl-6-trimethylsilanylethynyl-4,4-dimethyl-1,2,3,4-tetrahydro-  
20 quinoline (Intermediate 52)

21 Following general procedure D and using 6-bromo-1-cyclopropyl-4,4-  
22 dimethyl-1,2,3,4-tetrahydro quinoline (**Intermediate 51**, 0.8g, 2.86mmol),  
23 (trimethylsilyl)acetylene (5mL, 35mmol), triethyl amine (10mL), anhydrous  
24 tetrahydrofuran, copper(I)iodide (0.080g, 0.42mmol) and  
25 dichlorobis(triphenylphosphine)palladium(II) (0.240g, 0.34mmol), the title  
26 compound was obtained as an oil (0.67g, 79%).

27 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.33 (d, 1H, *J* = 1.8Hz), 7.22 (dd, 1H, *J* = 2.1,  
28 8.5Hz), 7.06 (d, 1H, *J* = 8.5Hz), 3.27 (t, 2H, *J* = 5.9Hz), 2.37-2.31 (m, 1H),

1 1.70 (t, 2H,  $J = 6.0\text{Hz}$ ), 1.28 (s, 6H), 0.89-0.82 (m, 2H), 0.66-0.60 (m, 2H),  
2 0.28 (s, 9H).

3 1-Cyclopropyl-6-ethynyl-4,4-dimethyl-1,2,3,4-tetrahydroquinoline:  
4 **(Intermediate 53)**

5 Following general procedure E and using 1-cyclopropyl-6-  
6 trimethylsilanylethynyl-4,4-dimethyl-1,2,3,4-tetrahydroquinoline  
7 **(Intermediate 52, 0.40g, 1.34mmol)**, methanol and potassium carbonate  
8 (0.2g, 1.47mmol) followed by flash column chromatography over silica gel  
9 (230-400 mesh) using 2% ethyl acetate in hexane as the eluent, the title  
10 compound was obtained as an oil (0.17g, 56%).

11  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.38 (d, 1H,  $J = 2.1\text{Hz}$ ), 7.27 (dd, 1H,  $J = 2.1$ ,  
12 8.5Hz), 7.11 (d, 1H,  $J = 8.5\text{Hz}$ ), 3.30 (t, 2H,  $J = 6.0\text{Hz}$ ), 3.02 (s, 1H), 2.40-  
13 2.34 (m, 1H), 1.74 (t, 2H,  $J = 6.0\text{Hz}$ ), 1.30 (s, 6H), 0.93-0.85 (m, 2H), 0.70-  
14 0.63 (m, 2H).

15 4-(1-Cyclopropyl-4,4-dimethyl-1,2,3,4-tetrahydro-quinolin-6-yl-ethynyl)-  
16 benzoic acid ethyl ester **(Compound 61, General Formula 7)**

17 Following general procedure F and using 1-cyclopropyl-6-ethynyl-4,4-  
18 dimethyl-1,2,3,4-tetrahydro quinoline **(Intermediate 53, 0.11g, 0.43mmol)**,  
19 ethyl-4-iodo-benzoate **(Reagent A, 0.11g, 0.9mmol)**, triethyl amine (3mL),  
20 tetrahydrofuran(3mL), copper(I)iodide(0.02g, 0.1mmol) and  
21 dichlorobis(triphenylphosphine)palladium(II) (0.060g, 0.085mmol) followed  
22 by flash column chromatography over silica gel (230-400 mesh) using 5-10%  
23 ethyl acetate in hexane as the eluent, the title compound was obtained (0.05g,  
24 31%).

25  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.99 (d, 2H,  $J = 8.2\text{Hz}$ ), 7.54 (d, 2H,  $J =$   
26 8.2Hz), 7.37 (d, 1H,  $J = 2.1\text{Hz}$ ), 7.26 (dd, 1H,  $J = 2.1$ , 8.5Hz), 7.10 (d, 1H,  $J =$   
27 8.8Hz), 4.37 (q, 2H,  $J = 7.1\text{Hz}$ ), 3.28 (t, 2H,  $J = 6.0\text{Hz}$ ), 2.40-2.33 (m, 1H),  
28 1.71 (t, 2H,  $J = 5.8\text{Hz}$ ), 1.40 (t, 3H,  $J = 7.0\text{Hz}$ ), 1.27 (s, 6H), 0.94-0.82 (m,  
29 2H), 0.65-0.60 (m, 2H).

1 4-(1-Cyclopropyl-4,4-dimethyl-1,2,3,4-tetrahydroquinolin-6-yl-ethynyl)-  
2 benzoic acid (Compound 62, General Formula 7)

3       Following general procedure L and using 4-(1-cyclopropyl-4,4-  
4 dimethyl-1,2,3,4-tetrahydro-quinolin-6-ylethynyl)-benzoic acid ethyl ester  
5 (**Compound 61**, 0.05g, 0.13mmol), 5mL of ethanol and 5M sodium hydroxide  
6 solution (2mL) followed by recrystallization from hot ethyl acetate, the title  
7 compound was obtained as a solid (0.030g, 64%).

8 <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>): δ 7.92 (d, 2H, J = 8.2Hz), 7.57 (d, 2H, J =  
9 8.2Hz), 7.33 (d, 1H, J = 1.9Hz), 7.23 (dd, 1H, J = 1.9, 8.5Hz), 7.06 (d, 1H, J =  
10 8.8Hz), 3.25 (t, 2H, J = 5.8Hz), 2.41-2.34 (m, 1H), 1.64 (t, 2H, J = 5.6Hz),  
11 1.21 (s, 6H), 0.87-0.81 (m, 2H), 0.59-0.54 (m, 2H).

12 [4-(1-Cyclopropyl-4,4-dimethyl-1,2,3,4-tetrahydro-quinolin-6-yl-  
13 ethynyl)phenyl] acetic acid methyl ester (Compound 63, General Formula  
14 7)

15       Following general procedure F and using 1-cyclopropyl-6-ethynyl-4,4-  
16 dimethyl-1,2,3,4-tetrahydro quinoline (**Intermediate 53**, 0.05g, 0.22mmol),  
17 methyl-4-iodo-phenyl acetate (**Reagent B**, 0.055g, 0.2mmol), triethyl amine  
18 (5mL), tetrahydrofuran, copper(I)iodide(0.025g, 0.13mmol) and  
19 dichlorobis(triphenylphosphine)palladium(II) (0.75g, 0.11mmol) followed  
20 preparative normal phase HPLC using 10 % ethyl acetate in hexane as the  
21 mobile phase, the title compound was obtained (0.089g, 100%).

22 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.47 (d, 2H, J = 8.8Hz), 7.45 (d, 1H, J =  
23 1.8Hz), 7.35-7.22 (m, 2H), 7.10 (d, 2H, J = 8.8Hz), 3.70 (s, 3H), 3.63 (s, 2H),  
24 3.27 (t, 2H, J = 6.0Hz), 2.37-2.31 (m, 1H), 1.71 (t, 2H, J = 6.0Hz), 1.27 (s,  
25 6H), 0.89-0.81 (m, 2H), 0.65-0.60 (m, 2H).

26 [4-(1-Cyclopropyl-4,4-dimethyl-1,2,3,4-tetrahydro-quinolin-6-yl-ethynyl)-2-  
27 fluoro-phenyl] acetic acid ethyl ester (Compound 64, General Formula 7)

28       Following general procedure F and using 1-cyclopropyl-6-ethynyl-4,4-  
29 dimethyl-1,2,3,4-tetrahydro quinoline (**Intermediate 53**, 0.11g, 0.49mmol),

1 ethyl-2-fluoro-4-iodo-phenyl acetate (**Reagent C**, 0.11g, 0.9mmol), triethyl  
2 amine (3mL), tetrahydrofuran(3mL), copper(I)iodide(0.06g, 0.32mmol) and  
3 dichlorobis(triphenylphosphine)palladium(II) (0.25g, 0.36mmol) followed by  
4 flash column chromatography over silica gel (230-400 mesh) using 10 % ethyl  
5 acetate in hexane as the eluent, the title compound was obtained (0.1g, 51%).  
6 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.34 (d, 1H, *J* = 2.1Hz), 7.25-7.17 (m, 3H),  
7 7.09 (d, 2H, *J* = 8.8Hz), 4.17 (q, 2H, *J* = 7.1Hz), 3.65 (s, 2H), 3.27 (t, 2H, *J* =  
8 6.0Hz), 2.38-2.31 (m, 1H), 1.69 (t, 2H, *J* = 6.0Hz), 1.27 (s, 6H), 1.25 (t, 3H, *J* =  
9 = 7.1Hz), 0.88-0.81 (m, 2H), 0.65-0.59 (m, 2H).

10 N-(4-Bromophenyl)-N-methyl-3-methyl-2-butenamide (**Intermediate 54**)

11 3,3-Dimethylacryloyl chloride (3mL, 27mmol) was added to a solution  
12 of 4-bromo-N-methyl-aniline (4.55g, 25mmol) in 150mL of dichloromethane  
13 followed after 5 minutes by triethyl amine (5mL, 33mmol). After 2.5h at  
14 ambient temperature, the reaction mixture was washed with water and the  
15 organic phase was dried over anhydrous sodium sulfate and evaporated in  
16 vacuo to afford the title product as a brown oil in quantitative yield.  
17 <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 1.71 (s, 3H), 2.11(s, 3H), 3.28(s, 3H), 5.47(s,  
18 1H), 7.05(d, *J* = 8.5Hz, 2H), 7.50(d, *J* = 8.2Hz, 2H).

19 6-Bromo-1,4,4-trimethyl-2-oxo-1,2,3,4-tetrahydroquinoline (**Intermediate 55**)

20 N-(4-bromophenyl)-N-methyl-3-methyl-2-butenamide  
21 (**Intermediate 54**, 6.42g, 24mmol) was heated to 130°C and aluminum  
22 chloride (5g, 37.4mmol) was added in portions over 0.5h. The reaction  
23 mixture was stirred for 1 hour at the same temperature and then cooled to  
24 room temperature. Ice was added cautiously to the solid, followed by ~200mL  
25 of iced water. The reaction mixture was then extracted with ether (x2) and  
26 dichloromethane (x1) and the combined organic phase was dried over  
27 anhydrous magnesium sulfate and evaporated in *vacuo* to yield a brown solid.  
28 The solid was treated with hexane-dichloromethane and filtered to afford 1.7g  
29 of product. The mother liquor was evaporated and purified by flash column

1 chromatography on silica gel (230-400 mesh) to afford 2.9g of the title  
2 compound as a solid (total 72%).  
3 <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 1.29(s, 6H), 2.49(s, 2H), 3.36(s, 3H), 6.87(d, *J*  
4 = 8.2Hz, 1H), 7.36(dd, *J* = 2.0, 8.5Hz, 1H), 7.39(d, *J* = 2.0Hz, 1H).  
5 6-Bromo-1,4,4-trimethylspiro[2H-1-1,2,3,4-tetrahydroquinoline-2,1'-  
6 cyclopropane] (**Intermediate 56**)  
7 A stirred, cooled (-78°C) 3M solution of ethyl magnesium bromide in  
8 ether (8.1mL, 24.25mmol) under argon was treated with anhydrous  
9 tetrahydrofuran (20mL) followed by a solution of titanium tetra-*iso*-propoxide  
10 (3.15mL, 10.2mmol) in tetrahydrofuran (10mL). A solution of 6-bromo-1,4,4-  
11 trimethyl-2-oxo-1,2,3,4-tetrahydroquinoline (**Intermediate 55**, 2.6g,  
12 9.7mmol) was cannulated into the reaction mixture and the solution was  
13 allowed to warm to room temperature overnight. It was then cooled in an ice-  
14 bath, quenched with saturated aqueous ammonium chloride solution, filtered  
15 over celite and the aqueous phase was extracted with diethyl ether (x2). The  
16 combined organic phase was dried over anhydrous magnesium sulfate, filtered  
17 and evaporated in *vacuo* to afford an orange oil. Flash column  
18 chromatography over silica gel (230-400 mesh) using 2-4% ethyl acetate in  
19 hexane as the eluent afforded the title compound as an oil which was ~70%  
20 pure (1.7g, 63%) and 0.5g of recovered starting material.  
21 <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 0.58(t, *J* = 6.0Hz, 2H), 0.91(t, *J* = 6.0Hz, 2H),  
22 1.35 (s, 6H), 1.70(s, 2H), 2.68 (s, 3H), 6.59 (d, *J* = 8.8Hz, 1H), 7.16(dd, *J* =  
23 2.3, 8.8Hz, 1H), 7.33(d, *J* = 2.3Hz, 1H).  
24 1,4,4-Trimethyl-6-(trimethylsilyl)ethynylspiro[2H-1-1,2,3,4-  
25 tetrahydroquinoline-2,1'-cyclopropane] (**Intermediate 57**)  
26 Following general procedure D and using 6-bromo-1,4,4-  
27 trimethylspiro[2H-1-1,2,3,4-tetrahydroquinoline-2,1'-cyclopropane]  
28 (**Intermediate 56**, 0.56g, 2mmol), (trimethylsilyl)acetylene (1.13mL, 8mmol),  
29 triethyl amine (4mL), anhydrous tetrahydrofuran (5mL), copper(I)iodide

1 (0.08g, 0.4mmol) and dichlorobis(triphenylphosphine)palladium(II) (0.28g,  
2 0.4mmol), followed by flash column chromatography over silica gel (230-400  
3 mesh) using hexane-2% ethyl acetate in hexane as the eluent, the title  
4 compound was obtained as an oil (0.42g, 70%).

5 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 0.023(s, 9H), 0.33(t, *J* = 6.1Hz, 2H), 0.71(t, *J*  
6 = 6.1Hz, 2H), 1.10(s, 6H), 1.45(s, 2H), 2.41 (s, 3H), 6.31(d, *J* = 8.5Hz, 1H),  
7 6.96 (dd, *J* = 2.1, 8.5Hz, 1H), 7.10(d, *J* = 2.1Hz, 1H).

8 Benzoic acid, 4-[(1,4,4-trimethylspiro[2*H*-1-1,2,3,4-tetrahydroquinoline-2,1'-  
9 cyclopropane]-6-yl)ethynyl]-ethyl ester (Compound 65, General Formula 1)

10 Following general procedure E and using a solution of 1,4,4-trimethyl-  
11 6-(trimethylsilyl)ethynylspiro[2*H*-1-1,2,3,4-tetrahydroquinoline-2,1'-  
12 cyclopropane] (Intermediate 57, 0.416g, 1.4mmol), methanol (10mL), ethyl  
13 acetate (2mL) and potassium carbonate (1.08g, mmol) a silyl deprotected  
14 acetylenic intermediate was obtained which was used directly for the next step  
15 (0.25g, 79%). Following general procedure F and using part of the acetylenic  
16 intermediate obtained as above (0.11g, 0.5mmol), ethyl-4-iodo benzoate  
17 (Reagent A, 0.112g, 0.4mmol), triethyl amine (1mL), tetrahydrofuran  
18 (2.5mL), copper(I)iodide (0.050g, 0.26mmol) and  
19 tetrakis(triphenylphosphine)palladium(0)(0.096g, 0.17mmol) followed by  
20 flash column chromatography over silica gel (230-400 mesh) using 8% ethyl  
21 acetate in hexane as the eluent and preparative HPLC on Partisil 10 silica  
22 column using 10% ethyl acetate in hexane as the mobile phase, the title  
23 compound was obtained as a yellow oil (0.048g, 26%).

24 <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 0.60 (t, *J* = 6.1Hz, 2H), 0.99(t, *J* = 6.1Hz, 2H),  
25 1.37(s, 6H), 1.42(t, *J* = 7.0Hz, 3H), 1.73(s, 2H), 2.68(s, 3H), 4.40 (q, *J* =  
26 7.0Hz, 2H), 6.61(d, *J* = 8.8Hz, 1H), 7.28 (dd, *J* = 2.1, 8.5Hz, 1H), 7.42 (d, *J* =  
27 2.1Hz, 1H), 7.57(d, *J* = 8.2Hz, 2H), 8.01(d, *J* = 8.2Hz, 2H).

28 Benzoic acid, 4-[(1,4,4-trimethylspiro[2*H*-1-1,2,3,4-tetrahydroquinoline-2,1'-  
29 cyclopropane]-6-yl)ethynyl]- (Compound 66, General Formula 1)

1       Following general procedure I and using benzoic acid, 4-[(1,4,4-  
2 trimethylspiro[2*H*-1-1,2,3,4-tetrahydroquinoline-2,1'-cyclopropane]-6-  
3 yl)ethynyl]-ethyl ester (**Compound 65**, 0.03g, 0.08mmol), ethanol (2mL),  
4 tetrahydrofuran (2mL) and 1M aqueous sodium hydroxide solution (1mL), the  
5 title compound was obtained as a yellow solid (0.020g, 67%).  
6 <sup>1</sup>H-NMR (300 MHz, CD<sub>3</sub>COCD<sub>3</sub>): δ 0.60 (t, *J* = 5.8Hz, 2H), 1.03(t, *J* = 5.8Hz,  
7 2H), 1.34(s, 6H), 1.74(s, 2H), 2.69(s, 3H), 6.60(d, *J* = 8.5Hz, 1H), 7.23 (dd, *J*  
8 = 2.0, 8.4Hz, 1H), 7.39 (d, *J* = 2.0Hz, 1H), 7.58(d, *J* = 8.2Hz, 2H), 8.01(d, *J*  
9 = 8.2Hz, 2H).

#### 10 Esterification Methods:

##### 11 Method A:

12       The carboxylic acid was combined with a solution of the desired  
13 alcohol and concentrated sulfuric acid (20 to 1 v/v) and the resulting mixture  
14 or solution (0.75 to 1.0 M) heated to reflux overnight. The solution was  
15 cooled to room temperature, diluted with Et<sub>2</sub>O, and washed with H<sub>2</sub>O,  
16 saturated aqueous NaHCO<sub>3</sub>, and saturated aqueous NaCl before being dried  
17 over MgSO<sub>4</sub>. Concentration of the dry solution under reduced pressure  
18 afforded the desired carboxylic ester of sufficient purity to be used directly in  
19 the next reaction.

##### 20 Method B:

21       To a solution (0.67 to 1.0M) of the carboxylic acid in acetone was  
22 added 1.1equivalents of the desired alkyl halide and 1.0 equivalents of solid  
23 potassium carbonate. The resulting mixture was heated to reflux for 2h and  
24 then allowed to stir at room temperature overnight. The mixture was filtered  
25 and the filtrate concentrated under reduced pressure. The product was isolated  
26 from the residue by column chromatography using silica gel as the solid phase.

##### 27 Method C:

28       A solution (1M) of the carboxylic acid in thionyl chloride was heated at



1 reflux until analysis of a reaction aliquot by IR spectroscopy showed the  
2 absence of the aryl carboxylic acid carbonyl band ( 1705 - 1680  $\text{cm}^{-1}$ ). The  
3 solution was cooled to room temperature and concentrated under reduced  
4 pressure to give the crude acyl chloride.

5 The acyl chloride was dissolved in  $\text{CH}_2\text{Cl}_2$  and the resulting solution  
6 (0.5 to 0.75M) treated with 1.1 equivalents the desired alcohol and 2.0  
7 equivalents of pyridine. After stirring overnight at room temperature the  
8 solution was diluted with  $\text{Et}_2\text{O}$  and washed with  $\text{H}_2\text{O}$ , 10% aqueous  $\text{HCl}$ ,  
9 saturated aqueous  $\text{NaHCO}_3$ , and saturated aqueous  $\text{NaCl}$  before being dried  
10 over  $\text{Na}_2\text{SO}_4$ . Concentration of the dry solution under reduced pressure  
11 followed by column chromatography afforded the desired ester.

12 GENERAL PROCEDURE 1 (preparation of Enol ethers):

13 A solution (0.35 M) of the aryl ester in anhydrous THF was cooled to 0  
14  $^\circ\text{C}$  and treated with 1.0 equivalents of Tebbe's Reagent ( $[\mu\text{-chloro-}\mu\text{-}$   
15  $\text{methylene[bis(cyclopentadienyl)titanium]-dimethylaluminum}]$  0.5 M in  
16 toluene). After 30 minutes the solution was warmed to room temperature and  
17 stirred for 30 minutes before being carefully added to a 0.1 N  $\text{NaOH}$  solution  
18 at 0  $^\circ\text{C}$ . This mixture was treated with hexanes and the solids removed by  
19 filtration through a pad of Celite. The solids were washed with hexanes and  
20 the filtrate passed through a second pad of Celite to remove any newly formed  
21 solids. The organic layer was dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated under reduced  
22 pressure. The desired enol ether was isolated from the residue by column  
23 chromatography using 1-2% of  $\text{Et}_3\text{N}$  added to the eluant. (note: prolonged  
24 exposure of the product to the column can result in hydrolysis and formation  
25 of the corresponding methyl ketone.)

26 GENERAL PROCEDURE 2 (cyclopropanation of the enol ethers):

27 To a solution (0.3 M) of the enol ether in anhydrous  $\text{Et}_2\text{O}$  was added  
28 2.0 equivalent of  $\text{Et}_2\text{Zn}$  (as a solution in hexanes) and 2.0 equivalents of  $\text{CH}_2\text{I}_2$ .

1 The resulting solution was heated to reflux until analysis of a reaction aliquot  
2 (by TLC or  $^1\text{H}$  NMR) indicated that all of the starting enol ether had been  
3 consumed. (note: Additional equal amounts of  $\text{Et}_2\text{Zn}$  and  $\text{CH}_2\text{I}_2$  can be added  
4 to drive the reaction to completion.) Upon cooling to room temperature the  
5 reaction was carefully quenched by the addition of saturated aqueous  $\text{NH}_4\text{Cl}$ .  
6 The resulting mixture is extracted with  $\text{Et}_2\text{O}$  and the combined organic layers  
7 washed with  $\text{H}_2\text{O}$  and saturated aqueous  $\text{NaCl}$  before being dried over  $\text{Na}_2\text{SO}_4$   
8 and concentrated under reduced pressure. The product is isolated from the  
9 residue by column chromatography.

10 1-Bromo-4-(1-methoxyvinyl)-benzene: (Intermediate 58)

11 Using General Procedure 1; methyl 4-bromo-benzoate (600.0 mg, 2.78  
12 mmols), and 5.6 mL of Tebbe's Reagent (794.0 mg, 2.78 mmols) afforded  
13 420.0 mg (70%) of the title compound as a colorless oil after column  
14 chromatography (100% hexanes).  
15  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 7.48 - 7.45 (4H, m), 4.64 (1H, d,  $J = 2.9$  Hz), 4.23 (1H, d,  
16  $J = 2.9$  Hz), 3.73 (3H, s).

17 1-Bromo-4-(1-methoxycyclopropyl)-benzene (Intermediate 59)

18 Using General Procedure 2; 1-bromo-4-(1-methoxyvinyl)-benzene  
19 (Intermediate 58, 410.0 mg, 1.92 mmols),  $\text{Et}_2\text{Zn}$  (711.3 mg, 5.76 mmols),  
20 and  $\text{CH}_2\text{I}_2$  (1.54 g, 5.76 mmols) in 4.0 mL  $\text{Et}_2\text{O}$  afforded 300.0 mg (69%) of  
21 the title compound as a colorless oil after chromatography (0-3%  $\text{EtOAc}$  -  
22 hexanes).

23  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 7.46 (2H, d,  $J = 8.5$  Hz), 7.18 (2H, d,  $J = 8.5$  Hz), 3.21  
24 (3H, s), 1.19 (2H, m), 0.94 (2H, m).

25 [4-(1-Methoxycyclopropyl)-phenylethynyl]-trimethylsilane (Intermediate  
26 60)

27 Using General Procedure D; 1-bromo-4-(1-methoxycyclopropyl)-  
28 benzene (Intermediate 59, 300.0 mg, 1.32 mmol) in triethylamine (4 mL) and

1 anhydrous tetrahydrofuran (4 mL) was treated with copper(I)iodide (93.0 mg,  
2 0.13 mmol) and then sparged with argon for 5 minutes. Trimethylsilyl  
3 acetylene (1.39 g, 14.2 mmols) was then added followed by  
4 dichlorobis(triphenylphosphine)palladium(II) (93.0 mg, 0.13 mmol). The  
5 resulting reaction mixture was heated to 70 °C for 60h. The title compound  
6 (286.0 mg, 90%) was isolated by chromatography (0 - 3% EtOAc - hexanes).  
7 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.35 (2H, d, J = 7.2 Hz), 7.14 (2H, d, J = 7.2 Hz), 3.14  
8 (3H, s), 1.14 (2H, m), 0.88 (2H, m), 0.17 (9H, s).

9 1-Ethynyl-4-(1-methoxycyclopropyl)-benzene (Intermediate 61)

10 Using General Procedure E; [4-(1-methoxycyclopropyl)-  
11 phenylethynyl]-trimethylsilane (Intermediate 60, 285.0 mg, 1.18 mmols) in  
12 methanol (10mL) was treated with potassium carbonate (100.0 mg, 0.72  
13 mmol) and stirred overnight at ambient temperature. The crude alkyne (220  
14 mg, 100%) was used directly in the next reaction.  
15 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.46 (2H, d, J = 8.2 Hz), 7.24 (2H, d, J = 8.2 Hz), 3.23  
16 (3H, s), 3.06 (1H, s), 1.22 (2H, m), 0.98 (2H, m).

17 Ethyl 4-[4-(1-methoxycyclopropyl)-phenylethynyl]-benzoate (Compound 67,

18 **General Formula 2)**

19 Using General Procedure F; 1-ethynyl-4-(1-methoxycyclopropyl)-  
20 benzene (Intermediate 61, 100.0 mg, 0.47 mmol) and ethyl-4-iodo benzoate  
21 (Reagent A, 141.0 mg, 0.51 mmol) in triethyl amine (6 mL) was treated with  
22 copper(I)iodide (30.0 mg, 0.16 mmol) and sparged with argon for 5 minutes.  
23 Dichlorobis(triphenylphosphine)palladium(II) (109 mg, 0.16 mmol) was added  
24 and the reaction mixture was stirred overnight at room temperature. Column  
25 chromatography (2-5% EtOAc - hexanes) afforded 135.0 mg (90%) of the title  
26 compound as an orange solid.  
27 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 8.02 (2H, d, J = 8.2 Hz), 7.58 (2H, d, J = 8.8 Hz), 7.52  
28 (2H, d, J = 8.2 Hz), 7.28 (2H, d, J = 8.8 Hz), 4.39 (2H, q, J = 7.1 Hz), 3.25

1 (3H, s), 1.40 (3H, t, J = 7.1 Hz), 1.23 (2H, m), 1.00 (2H, m).

2 Methyl {4-[4-(1-methoxycyclopropyl)-phenylethynyl]-phenyl}-acetate

3 **(Compound 68, General Formula 2)**

4 Using General Procedure F; 1-ethynyl-4-(1-methoxycyclopropyl)-  
5 benzene (**Intermediate 61**, 120.0 mg, 0.56 mmol) and methyl-(4-iodophenyl)-  
6 acetate (**Reagent B**, 154.0 mg, 0.56 mmol) in triethyl amine (6 mL) was  
7 treated with copper(I)iodide (35.0 mg, 0.19 mmol) and sparged with argon for  
8 5 minutes. Dichlorobis(triphenylphosphine)palladium(II) (130 mg, 0.19  
9 mmol) was added and the reaction mixture was stirred overnight at room  
10 temperature. Column chromatography (2-8% EtOAc - hexanes) afforded  
11 140.0 mg (78%) of the title compound as an orange solid.

12 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.50 (4H, d, J = 8.1 Hz), 7.28 (4H, d, J = 8.1 Hz), 3.76  
13 (3H, s), 3.64 (2H, s), 3.25 (3H, s), 1.22 (2H, m), 0.99 (2H, m).

14 4-[4-(1-Methoxycyclopropyl)-phenylethynyl]-benzoic acid (**Compound 69**,  
15 **General Formula 2**)

16 Using General Procedure I; a solution of ethyl 4-[4-(1-  
17 methoxycyclopropyl)-phenylethynyl]-benzoate (**Compound 67**, 110.0 mg,  
18 0.34 mmol) in ethanol (3 mL) and tetrahydrofuran (3 mL) was treated with  
19 NaOH (160.0 mg, 4.0 mmols, 2.0 mL of a 2N aqueous solution) and stirred  
20 overnight at room temperature. Work-up afforded 85.0 mg (86%) of the title  
21 compound as an orange solid.

22 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 8.05 (2H), 7.66 (2H), 7.56 (2H, d, J = 8.5 Hz), 7.35 (2H,  
23 d, J = 8.6 Hz), 3.22 (3H, s), 1.21 (2H, m), 1.01 (2H, m).

24 {4-[4-(1-Methoxycyclopropyl)-phenylethynyl]-phenyl}-acetic acid  
25 **(Compound 70, General Formula 2)**

26 Using General Procedure I; a solution of methyl {4-[4-(1-  
27 methoxycyclopropyl)-phenylethynyl]-phenyl}-acetate (**Compound 68**, 100.0  
28 mg, 0.31 mmol) in ethanol (3 mL) and tetrahydrofuran (3 mL) was treated

1 with NaOH (160.0 mg, 4.0 mmols, 2.0 mL of a 2N aqueous solution) and  
2 stirred overnight at room temperature. Work-up afforded 80.0 mg (84%) of  
3 the title compound as an orange solid.  
4 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.49 (4H), 7.27 (4H), 3.66 (2H, s), 3.25 (3H, s), 1.22 (2H,  
5 m), 0.99 (2H, m).

6 Isopropyl 4-bromobenzoate (Intermediate 62)

7 Using General Esterification Procedure A; 4-bromobenzoic acid (1.50  
8 g, 7.46 mmols) was combined with isopropyl alcohol to give 1.76 g (97%) of  
9 the title compound as a colorless oil.

10 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.90 (2H, d, J = 8.5 Hz), 7.57 (2H, d, J = 8.5 Hz),  
11 5.24 (1H, septet, J = 6.2 Hz), 1.37 (6H, d, J = 6.2 Hz).

12 1-Bromo-4-(1-isopropoxyvinyl)-benzene (Intermediate 63)

13 Using General Procedure 1; isopropyl 4-bromobenzoate (**Intermediate**  
14 **62**, 780.0 mg, 3.20 mmols) and 6.4 mL of Tebbe's Reagent (910.7 mg, 3.20  
15 mmols) afforded 328.0 mg (43%) of the title compound as a colorless oil after  
16 column chromatography (100% hexanes).

17 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.46 (4H, m), 4.66 (1H, d, J = 2.6 Hz), 4.40 (1H, septet, J  
18 = 6.2 Hz), 4.21 (1H, d, J = 2.6 Hz), 1.34 (6H, d, J = 6.2 Hz).

19 1-Bromo-4-(1-isopropoxycyclopropyl)-benzene (Intermediate 64)

20 Using General Procedure 2; 1-bromo-4-(1-isopropoxyvinyl)-benzene  
21 (**Intermediate 63**, 328.0 mg, 1.36 mmols), Et<sub>2</sub>Zn (335.9 mg, 2.72 mmols),  
22 and CH<sub>2</sub>I<sub>2</sub> (728.0 mg, 2.72 mmols) in 4.0 mL Et<sub>2</sub>O afforded 240.0 mg (70%)  
23 of the title compound as a colorless oil after chromatography (3% EtOAc -  
24 hexanes).

25 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.43 (2H, d, J = 8.5 Hz), 7.27 (2H, d, J = 8.5 Hz), 3.70  
26 (1H, septet, J = 6.2 Hz), 1.18 (2H, m), 1.06 (6H, d, J = 6.2 Hz), 0.91 (2H, m).

27 [4-(1-Isopropoxycyclopropyl)-phenylethynyl]-trimethylsilane (Intermediate  
28 **65)**

1       Using General Procedure D; 1-bromo-4-(1-isopropoxycyclopropyl)-  
2 benzene (**Intermediate 64**, 240.0 mg, 0.94 mmol) in triethylamine (8 mL) was  
3 treated with copper(I)iodide (18.0 mg, 0.094 mmol) and then sparged with  
4 argon for 5 minutes. Trimethylsilyl acetylene (0.70 g, 7.1 mmols) was then  
5 added followed by dichlorobis-(triphenylphosphine)palladium(II) (66.0 mg,  
6 0.094 mmol). The resulting reaction mixture was heated to 70 °C for 5 days.  
7 The title compound (250.0 mg, 98%) was isolated by chromatography (0 - 3%  
8 EtOAc - hexanes) as an orange oil.  
9 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.41 (2H, d, J = 7.9 Hz), 7.31 (2H, d, J = 7.9 Hz), 3.70  
10 (1H, septet, J = 6.2 Hz), 1.18 (2H, m), 1.05 (6H, d, J = 6.2 Hz), 0.93 (2H, m),  
11 0.94 (9H, s).

12 1-Ethynyl-4-(1-isopropoxycyclopropyl)-benzene (**Intermediate 66**)

13       Using General Procedure E; [4-(1-isopropoxycyclopropyl)-  
14 phenylethynyl]-trimethylsilane (**Intermediate 65**, 260.0 mg, 0.96 mmol) in  
15 methanol (10 mL) was treated with potassium carbonate (100.0 mg, 0.72  
16 mmol) and stirred overnight at ambient temperature. The crude alkyne (220  
17 mg, 100%) was used directly in the next reaction.  
18 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.45 (2H, d, J = 8.8 Hz), 7.35 (2H, d, J = 8.8 Hz), 3.72  
19 (1H, septet, J = 6.2 Hz), 3.06 (1H, s), 1.20 (2H, m), 1.07 (6H, d, J = 6.2 Hz),  
20 0.95 (2H, m).

21 Ethyl 4-[4-(1-isopropoxycyclopropyl)-phenylethynyl]-benzoate (**Compound**  
22 **71, General Formula 2)**

23       Using General Procedure F; 1-ethynyl-4-(1-isopropoxycyclopropyl)-  
24 benzene (**Intermediate 66**, 114.0 mg, 0.57 mmol) and ethyl-4-iodo benzoate  
25 (**Reagent A**, 731.0 mg, 0.63 mmol) in triethylamine (8 mL) was treated with  
26 copper(I)iodide (36.0 mg, 0.19 mmol) and sparged with argon for 5 minutes.  
27 Dichlorobis(triphenylphosphine)palladium(II) (133 mg, 0.19 mmol) was added  
28 and the reaction mixture was stirred overnight at room temperature. Column

1 chromatography (2-4% EtOAc - hexanes) afforded 151.0 mg (76%) of the title  
2 compound as an orange solid.

3 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 8.02 (2H, d, J = 7.6 Hz), 7.58 (2H, d, J = 7.6 Hz), 7.50  
4 (2H, d, J = 7.8 Hz), 7.39 (2H, d, J = 7.8 Hz), 4.39 (2H, q, J = 7.1 Hz), 3.74  
5 (1H, septet, J = 6.2 Hz), 1.40 (3H, t, J = 7.1 Hz), 1.22 (2H, m), 1.08 (6H, d, J =  
6 6.2 Hz), 0.97 (2H, m).

7 Methyl {4-[4-(1-isopropoxycyclopropyl)-phenylethynyl]-phenyl}-acetate  
8 **(Compound 72, General Formula 2)**

9 Using General Procedure F; 1-ethynyl-4-(1-isopropoxycyclopropyl)-  
10 benzene (**Intermediate 66**, 95.0 mg, 0.45 mmol) and methyl-(4-iodophenyl)-  
11 acetate (**Reagent B**, 131.0 mg, 0.45 mmol) in triethylamine (6 mL) was treated  
12 with copper(I)iodide (30.0 mg, 0.16 mmol) and sparged with argon for 5  
13 minutes. Dichlorobis(triphenylphosphine)palladium(II) (111 mg, 0.16 mmol)  
14 was added and the reaction mixture was stirred overnight at room temperature.  
15 Column chromatography (2-8% EtOAc - hexanes) afforded 110.0 mg (70%)  
16 of the title compound as an orange oil.

17 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.20 (4H), 7.08 (2H, d, J = 7.0 Hz), 6.97 (2H, d, J = 7.9  
18 Hz), 3.45 (1H, septet, J = 6.2 Hz), 3.41 (3H, s), 3.35 (2H, s), 0.91 (2H, m),  
19 0.79 (6H, d, J = 6.2 Hz), 0.68 (2H, m).

20 4-[4-(1-Isopropoxycyclopropyl)-phenylethynyl]-benzoic acid (**Compound**  
21 **73, General Formula 2)**

22 Using General Procedure I; a solution of ethyl 4-[4-(1-  
23 isopropoxycyclopropyl)-phenylethynyl]-benzoate (**Compound 71**, 110.0 mg,  
24 0.32 mmol) in ethanol (3 mL) and tetrahydrofuran (3 mL) was treated with  
25 NaOH (120.0 mg, 3.0 mmols, 3.0 mL of a 1N aqueous solution) and stirred  
26 overnight at room temperature. Work-up afforded 89.0 mg (88%) of the title  
27 compound as a yellow solid.

28 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 8.06 (2H, d, J = 8.2 Hz), 7.66 (2H, d, J = 8.2 Hz), 7.55

1 (2H, d, J = 8.2 Hz), 7.46 (2H, d, J = 8.2 Hz), 3.73 (1H, septet, J = 6.2 Hz), 1.18  
2 (2H, m), 1.04 (6H, d, J = 6.2 Hz), 0.99 (2H, m).

3 {4-[4-(1-Isopropoxycyclopropyl)-phenylethynyl]-phenyl}-acetic acid

4 **(Compound 74, General Formula 2)**

5 Using General Procedure I; a solution of methyl {4-[4-(1-  
6 isopropoxycyclopropyl)-phenylethynyl]-phenyl}-acetate (**Compound 72**, 80.0  
7 mg, 0.23 mmol) in ethanol (3 mL) and tetrahydrofuran (3 mL) was treated  
8 with NaOH (80.0 mg, 2.0 mmols, 2.0 mL of a 1N aqueous solution) and  
9 stirred overnight at room temperature. Work-up afforded 48.0 mg (56%) of  
10 the title compound as a solid.

11 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.20 (2H, d, J = 8.2 Hz), 7.19 (2H, d, J = 8.8 Hz), 7.09  
12 (2H, d, J = 8.8 Hz), 6.98 (2H, d, J = 8.2 Hz), 3.46 (1H, septet, J = 6.2 Hz), 3.37  
13 (2H, s), 0.92 (2H, m), 0.79 (6H, d, J = 6.2 Hz), 0.67 (2H, m).

14 Benzyl 4-bromobenzoate (Intermediate 67)

15 Using General Esterification Method B; 4-bromobenzoic acid (2.01 g,  
16 10.0 mmols), benzyl bromide (1.89 g, 11.1 mmols), and K<sub>2</sub>CO<sub>3</sub> (1.40 g, 10.0  
17 mmols) afforded 2.33 g (80%) of the title compound as a colorless solid after  
18 column chromatography (3-10% EtOAc - hexanes).

19 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.89 (2H, d, J = 8.5 Hz), 7.52 (2H, d, J = 8.5 Hz), 7.43 -  
20 7.31 (5H), 5.33 (2H, s).

21 1-Bromo-4-(1-benzyloxyvinyl)-benzene (Intermediate 68)

22 Using General Procedure 1; benzyl 4-bromobenzoate (**Intermediate**  
23 **67**, 920.0 mg, 3.16 mmols) and 6.3 mL of Tebbe's Reagent (897.0 mg, 3.16  
24 mmols) afforded 640.0 mg (70%) of the title compound after column  
25 chromatography (100% hexanes).

26 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.55 - 7.35 (9H), 4.95 (2H, s), 4.73 (1H, d, J = 2.9 Hz),  
27 4.34 (1H, d, J = 2.9 Hz).

28 1-Bromo-4-(1-benzyloxycyclopropyl)-benzene (Intermediate 69)



1 Using General Procedure 2; 1-bromo-4-(1-benzyloxyvinyl)-benzene  
2 (**Intermediate 68**, 280.0 mg, 0.97 mmol), Et<sub>2</sub>Zn (247.0 mg, 2.0 mmols), and  
3 CH<sub>2</sub>I<sub>2</sub> (536.0 mg, 2.0 mmols) in 2.0 mL Et<sub>2</sub>O afforded 159.0 mg (53%) of the  
4 title compound as a colorless solid after chromatography (2-5% EtOAc -  
5 hexanes).

6 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.49 - 7.24 (9H), 4.41 (2H, s), 1.29 (2H, m), 1.00 (2H,  
7 m).

8 [4-(1-Benzyloxycyclopropyl)-phenylethynyl]-trimethylsilane (**Intermediate**  
9 **70**)

10 Using General Procedure D; 1-bromo-4-(1-benzyloxycyclopropyl)-  
11 benzene (**Intermediate 69**, 160.0 mg, 0.53 mmol) in triethylamine (5 mL) was  
12 treated with copper(I)iodide (10.0 mg, 0.05 mmol) and then sparged with  
13 argon for 5 minutes. Trimethylsilylacetylene (0.70 g, 7.1 mmols) was then  
14 added followed by dichlorobis-(triphenylphosphine)palladium(II) (37.0 mg,  
15 0.05 mmol). The resulting reaction mixture was heated to 70 °C for 5d. The  
16 title compound (150.0 mg, 83%) was isolated by chromatography (0 - 3%  
17 EtOAc - hexanes) as a pale-yellow oil.

18 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.21 (3H, m), 7.09 - 7.01 (6H, m), 4.18 (2H, s), 1.07 (2H,  
19 m), 0.79 (2H, m), 0.02 (9H, s).

20 1-Ethynyl-4-(1-benzyloxycyclopropyl)-benzene (**Intermediate 71**)

21 Using General Procedure E; [4-(1-benzyloxycyclopropyl)-  
22 phenylethynyl]-trimethylsilane (**Intermediate 70**, 150.0 mg, 0.47 mmols) in  
23 methanol (6 mL) was treated with potassium carbonate (100.0 mg, 0.72 mmol)  
24 and stirred overnight at ambient temperature. The crude alkyne (115 mg,  
25 100%) was used directly in the next reaction.

26 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.67 - 7.50 (2H, d, J = 8.2 Hz), 7.34 - 7.26 (7H, m), 4.43  
27 (2H, s), 3.07 (1H, s), 1.32 (2H, m), 1.04 (2H, m).

28 Ethyl 4-[4-(1-benzyloxycyclopropyl)-phenylethynyl]-benzoate (**Compound**

**1 75, General Formula 2)**

2       Using General Procedure F; 1-ethynyl-4-(1-benzyloxycyclopropyl)-  
3 benzene (**Intermediate 71**, 60.0 mg, 0.24 mmol) and ethyl-4-iodo benzoate  
4 (**Reagent A**, 72.0 mg, 0.26 mmol) in triethylamine (4 mL) was treated with  
5 copper(I)iodide (17.0 mg, 0.09 mmol) and sparged with argon for 5 minutes.  
6 Dichlorobis(triphenylphosphine)palladium(II) (61 mg, 0.09 mmol) was added  
7 and the reaction mixture was stirred overnight at room temperature. Column  
8 chromatography (2-4% EtOAc - hexanes) afforded 85.0 mg (91%) of the title  
9 compound as an orange oil.

10 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 8.03 (2H, d, J = 8.2 Hz), 7.62-7.54 (4H, m), 7.39-7.26  
11 (7H, m), 4.47 (2H, s), 4.40 (2H, q, J = 7.1 Hz), 1.42 (3H, t, J = 7.1 Hz), 1.36  
12 (2H, m), 1.07 (2H, m).

13 Methyl {4-[4-(1-benzyloxycyclopropyl)-phenylethynyl]-phenyl}-acetate

**14 (Compound 76, General Formula 2)**

15       Using General Procedure F; 1-ethynyl-4-(1-benzyloxycyclopropyl)-  
16 benzene (**Intermediate 71**, 60.0 mg, 0.20 mmol) and methyl-(4-iodophenyl)-  
17 acetate (**Reagent B**, 66.0 mg, 0.24 mmol) in triethylamine (5 mL) was treated  
18 with copper(I)iodide (15.0 mg, 0.08 mmol) and sparged with argon for 5  
19 minutes. Dichlorobis(triphenylphosphine)palladium(II) (56 mg, 0.08 mmol)  
20 was added and the reaction mixture was stirred overnight at room temperature.  
21 Column chromatography (2-7% EtOAc - hexanes) afforded 64.0 mg (81%) of  
22 the title compound as a yellow oil.

23 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.52-7.47 (4H, m), 7.37-7.25 (9H, m), 4.44 (2H, s), 3.70  
24 (3H, s), 3.64 (2H, s), 1.32 (2H, m), 1.06 (2H, m).

25 4-[4-(1-Benzyloxycyclopropyl)-phenylethynyl]-benzoic acid (**Compound 77**,

**26 General Formula 2)**

27       Using General Procedure I; a solution of ethyl 4-[4-(1-  
28 benzyloxycyclopropyl)-phenylethynyl]-benzoate (**Compound 75**, 78.0 mg,

1 0.20 mmol) in ethanol (3 mL) and tetrahydrofuran (3 mL) was treated with  
2 NaOH (80.0 mg, 2.0 mmols, 2.0 mL of a 1N aqueous solution) and stirred  
3 overnight at room temperature. Work-up afforded 65.0 mg (89%) of the title  
4 compound as a solid.

5 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.97 (2H, d, J = 8.5 Hz), 7.67 (2H, d, J = 8.7 Hz), 7.58  
6 (2H, d, J = 8.5 Hz), 7.41-7.28 (7H, m), 4.44 (2H, s), 1.33 (2H, m), 1.12 (2H,  
7 m).

8 {4-[4-(1-Benzyloxycyclopropyl)-phenylethynyl]-phenyl}-acetic acid  
9 **(Compound 78, General Formula 2)**

10 Using General Procedure I; a solution of methyl {4-[4-(1-  
11 benzyloxycyclopropyl)-phenylethynyl]-phenyl}-acetate (**Compound 76**, 45.0  
12 mg, 0.11 mmol) in ethanol (3 mL) and tetrahydrofuran (3 mL) was treated  
13 with NaOH (80.0 mg, 2.0 mmols, 2.0 mL of a 1N aqueous solution) and  
14 stirred overnight at room temperature. Work-up afforded 35.0 mg (81%) of  
15 the title compound as a pale-yellow solid.

16 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.49 (4H, m), 7.37-7.25 (9H, m), 4.44 (2H, s), 3.66 (2H,  
17 s), 1.32 (2H, m), 1.05 (2H, m).

18 Benzyl 4-bromo-2-methylbenzoate (**Intermediate 72**)

19 Using General Esterification Method C; 2-methyl-4-bromo-benzoic  
20 acid (2.15 g, 10.0 mmols) was refluxed for 3h with 10 mL SOCl<sub>2</sub>. The  
21 resulting solution concentrated under reduced pressure and the crude acyl  
22 chloride was combined with benzyl alcohol (1.08 g, 10.0mmols) and pyridine  
23 (1.6 mL, 20.0 mmols) to give the title compound (2.4 g, 80%) after work-up  
24 and column chromatography (2-5% EtOAc - hexanes) as a colorless oil.

25 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.81 (1H, d, J = 8.5 Hz), 7.41-7.33 (7H, m), 5.32 (2H, s),  
26 2.57 (3H, s).

27 4-Bromo-1-(1-benzyloxyvinyl)-2-methylbenzene (**Intermediate 73**)

28 Using General Procedure 1; benzyl 4-bromo-2-methylbenzoate

1 (Intermediate 72, 840.0 mg, 2.77 mmols) and 5.4 mL of Tebbe's Reagent  
2 (788.0 mg, 2.77 mmols) afforded 640.0 mg (76%) of the title compound after  
3 column chromatography (100% hexanes).  
4 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.38-7.19 (8H, m), 4.88 (2H, s), 4.45 (1H, d, J = 2.6 Hz),  
5 4.25 (2H, d, J = 2.6 Hz), 2.35 (3H, s).

6 4-Bromo-1-(1-benzyloxycyclopropyl)-2-methyl-benzene (Intermediate 74)

7 Using General Procedure 2; 4-bromo-1-(1-benzyloxyvinyl)-2-methyl-  
8 benzene (Intermediate 73, 400.0 mg, 1.32 mmols), Et<sub>2</sub>Zn (325.0 mg, 2.63  
9 mmols), and CH<sub>2</sub>I<sub>2</sub> (704.0 mg, 2.63 mmols) in 4 mL Et<sub>2</sub>O afforded 380.0 mg  
10 (90%) of the title compound as a colorless oil after chromatography (2-5%  
11 EtOAc - hexanes).

12 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.42-7.20 (8H, m), 4.31 (2H, s), 2.58 (3H, s), 1.25 (2H,  
13 m), 0.94 (2H, m).

14 [4-(1-Benzyloxycyclopropyl)-3-methyl-phenylethynyl]-trimethylsilane  
15 (Intermediate 75)

16 Using General Procedure D; 4-bromo-1-(1-benzyloxycyclopropyl)-2-  
17 methyl-benzene (Intermediate 74, 320.0 mg, 1.00 mmol) in triethylamine (8  
18 mL) was treated with copper(I)iodide (19.0 mg, 0.1 mmol) and then sparged  
19 with argon for 5 minutes. Trimethylsilylacetylene (0.70 g, 7.1 mmols) was  
20 then added followed by dichlorobis-(triphenylphosphine)palladium(II) (70.0  
21 mg, 0.05 mmol). The resulting reaction mixture was heated to 70 °C for 5d.  
22 The title compound (300.0 mg, 89%) was isolated by chromatography (0 - 2%  
23 EtOAc - hexanes).

24 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.34-7.13 (8H, m), 4.24 (2H, s), 2.52 (3H, s), 1.20 (2H,  
25 m), 0.88 (2H, m), 0.25 (9H, s).

26 4-Ethynyl-1-(1-benzyloxycyclopropyl)-2-methyl-benzene (Intermediate 76)

27 Using General Procedure E; [4-(1-benzyloxycyclopropyl)-3-methyl-  
28 phenylethynyl]-trimethylsilane (Intermediate 75, 300.0 mg, 0.95 mmols) in

1 methanol (6 mL) was treated with potassium carbonate (120.0 mg, 0.87 mmol)  
2 and stirred overnight at ambient temperature. The crude alkyne (185 mg,  
3 79%) was used directly in the next reaction.  
4 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.37-7.16 (8H, m), 4.27 (2H, s), 3.07 (1H, s), 2.55 (3H,  
5 s), 1.21 (2H, m), 0.92 (2H, m).

6 Ethyl 4-[4-(1-benzyloxycyclopropyl)-3-methyl-phenylethynyl]-benzoate  
7 **(Compound 79, General Formula 2)**

8 Using General Procedure F; 1-ethynyl-4-(1-benzyloxycyclopropyl)-3-  
9 methyl-benzene (**Intermediate 76**, 90.0 mg, 0.34 mmol) and ethyl-4-iodo  
10 benzoate (**Reagent A**, 95.0 mg, 0.34 mmol) in triethylamine (6 mL) was  
11 treated with copper(I)iodide (23.0 mg, 0.12 mmol) and sparged with argon for  
12 5 minutes. Dichlorobis(triphenylphosphine)palladium(II) (80 mg, 0.11 mmol)  
13 was added and the reaction mixture was stirred overnight at room temperature.  
14 Column chromatography (2-4% EtOAc - hexanes) afforded 68.0 mg (54%) of  
15 the title compound.

16 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 8.03 (2H, d, J = 8.2 Hz), 7.58 (2H, d, J = 8.2 Hz), 7.33-  
17 7.16 (8H, m), 4.39 (2H, q, J = 7.1 Hz), 4.29 (2H, s), 2.57 (3H, s), 1.40 (3H, t, J  
18 = 7.1 Hz), 1.22 (2H, m), 0.93 (2H, m).

19 Methyl {4-[4-(1-benzyloxycyclopropyl)-3-methyl-phenylethynyl]-phenyl}-  
20 acetate **(Compound 80, General Formula 2)**

21 Using General Procedure F; 1-ethynyl-4-(1-benzyloxycyclopropyl)-3-  
22 methyl-benzene (**Intermediate 76**, 90.0 mg, 0.34 mmol) and methyl-(4-  
23 iodophenyl)-acetate (**Reagent B**, 95.0 mg, 0.34 mmol) in triethylamine (5 mL)  
24 was treated with copper(I)iodide (22.0 mg, 0.11 mmol) and sparged with argon  
25 for 5 minutes. Dichlorobis(triphenylphosphine)palladium(II) (80 mg, 0.11  
26 mmol) was added and the reaction mixture was stirred overnight at room  
27 temperature. Column chromatography (2-4% EtOAc - hexanes) afforded 90.0  
28 mg (71%) of the title compound as a pale-yellow oil.

1 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.49 (2H, d, J = 8.2 Hz), 7.32-7.16 (10H, m), 4.28 (2H,  
2 s), 3.70 (3H, s), 3.64 (2H, s), 2.56 (3H, s), 1.22 (2H, m), 0.92 (2H, m).

3 4-[4-(1-Benzyloxycyclopropyl)-3-methyl-phenylethynyl]-benzoic acid

4 **(Compound 81, General Formula 2)**

5 Using General Procedure I; a solution of ethyl 4-[4-(1-  
6 benzyloxycyclopropyl)-3-methyl-phenylethynyl]-benzoate (**Compound 79**,  
7 68.0 mg, 0.17 mmol) in ethanol (3 mL) and tetrahydrofuran (3 mL) was  
8 treated with NaOH (360.0 mg, 9.0 mmols, 3.0 mL of a 3N aqueous solution)  
9 and stirred overnight at room temperature. Work-up afforded 48.0 mg (76%)  
10 of the title compound as a solid.

11 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 8.10 (2H, d, J = 8.1 Hz), 7.63 (2H, d, J = 8.1 Hz), 7.44-  
12 7.16 (8H, m), 4.29 (2H, m), 2.58 (3H, s), 1.24 (2H, m), 0.94 (2H, m).

13 {4-[4-(1-Benzyloxycyclopropyl)-3-methyl-phenylethynyl]-phenyl}-acetic acid

14 **(Compound 82, General Formula 2)**

15 Using General Procedure I; a solution of methyl {4-[4-(1-  
16 benzyloxycyclopropyl)-3-methyl-phenylethynyl]-phenyl}-acetate (**Compound**  
17 **80**, 75.0 mg, 0.18 mmol) in ethanol (3 mL) and tetrahydrofuran (3 mL) was  
18 treated with NaOH (120.0 mg, 3.0 mmols, 3.0 mL of a 1N aqueous solution)  
19 and stirred overnight at room temperature. Work-up afforded 30.0 mg (40%)  
20 of the title compound.

21 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.51 (2H, d, J = 8.2 Hz), 7.42 (1H, s), 7.33-7.17 (9H, m),  
22 4.36 (2H, s), 3.67 (2H, s), 2.57 (3H, s), 1.23 (2H, m), 0.94 (2H, m).

23 Isopropyl 3-methyl-4-bromobenzoate (Intermediate 77)

24 Using General Esterification Procedure A; 4-bromo-2-methylbenzoic  
25 acid (1.6 g, 7.4 mmols) was combined with isopropyl alcohol to give 1.5 g  
26 (79%) of the title compound as a colorless oil.

27 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.76 (1H, d, J = 8.2 Hz), 7.40 (1H, d, J = 7.4 Hz), 7.37  
28 (1H, dd, J = 1.4, 8.2 Hz), 5.23 (1H, septet, J = 6.2 Hz), 2.57 (3H, s), 1.37 (6H,

1 d, J = 6.2 Hz).

2 4-Bromo-1-(1-isopropoxyvinyl)-2-methyl-benzene (Intermediate 78)

3 Using General Procedure 1; isopropyl 2-methyl-4-bromobenzoate  
4 (**Intermediate 77**, 800.0 mg, 3.11 mmols) and 6.2 mL of Tebbe's Reagent  
5 (885.2 mg, 3.11 mmols) afforded 595.0 mg (75%) of the title compound as a  
6 colorless oil after column chromatography (100% hexanes).

7 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.31-7.25 (2H, m), 7.16 (1H, d, J = 8.2 Hz), 4.34 (1H,  
8 septet, J = 6.0 Hz), 4.31 (1H, d, J = 2.1 Hz), 4.18 (1H, d, J = 2.1 Hz), 2.33 (3H,  
9 s), 1.31 (6H, d, J = 6.0 Hz).

10 4-Bromo-1-(1-isopropoxycyclopropyl)-2-methyl-benzene (Intermediate 79)

11 Using General Procedure 2; 4-bromo-1-(1-isopropoxyvinyl)-2-methyl-  
12 benzene (**Intermediate 78**, 389.0 mg, 1.53 mmols), Et<sub>2</sub>Zn (376.6 mg, 3.05  
13 mmols), and CH<sub>2</sub>I<sub>2</sub> (817.0 mg, 3.05 mmols) in 3.0 mL Et<sub>2</sub>O afforded 340.0 mg  
14 (84%) of the title compound as a colorless oil after chromatography (3%  
15 EtOAc - hexanes).

16 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.33 (1H, d, J = 2.3 Hz), 7.24 (1H, dd, J = 2.3, 8.2 Hz),  
17 7.13 (1H, d, J = 8.2 Hz), 3.57 (1H, septet, J = 6.1 Hz), 2.49 (3H, s), 1.00 (2H,  
18 m), 0.97 (6H, d, J = 6.1 Hz), 0.82 (2H, m).

19 [4-(1-Isopropoxycyclopropyl)-3-methyl-phenylethynyl]-trimethylsilane  
20 (**Intermediate 80**)

21 Using General Procedure D; 4-bromo-1-(1-isopropoxycyclopropyl)-2-  
22 methyl-benzene (**Intermediate 79**, 250.0 mg, 0.95 mmol) in triethylamine (8  
23 mL) was treated with copper(I)iodide (19.0 mg, 0.10 mmol) and then sparged  
24 with argon for 5 minutes. Trimethylsilylacetylene (0.70 g, 7.1 mmols) was  
25 then added followed by dichlorobis-(triphenylphosphine)palladium(II) (70.0  
26 mg, 0.1 mmol). The resulting reaction mixture was heated to 70 °C for 5d.  
27 The title compound (250.0 mg, 91%) was isolated by chromatography (0 - 3%  
28 EtOAc - hexanes).

1 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.32-7.17 (3H, m), 3.56 (1H, septet, J = 6.2 Hz), 2.48  
2 (3H, s), 1.00 (2H, m), 0.95 (6H, d, J = 6.2 Hz), 0.83 (2H, m), 0.24 (9H, s).  
3 4-Ethynyl-1-(1-isopropoxycyclopropyl)-2-methyl-benzene (Intermediate 81)

4 Using General Procedure E; [4-(1-isopropoxycyclopropyl)-3-methyl-  
5 phenylethynyl]-trimethylsilane (**Intermediate 80**, 250.0 mg, 0.87 mmol) in  
6 methanol (10 mL) was treated with potassium carbonate (100.0 mg, 0.72  
7 mmol) and stirred overnight at ambient temperature. The crude alkyne (180  
8 mg, 98%) was used directly in the next reaction.

9 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.32 (1H, s), 7.23 (2H, m), 3.57 (1H, septet, J = 6.2 Hz),  
10 3.05 (1H, s), 2.50 (3H, s), 1.11 (2H, m), 0.96 (6H, d, J = 6.2 Hz), 0.83 (2H, m).  
11 Ethyl 4-[4-(1-isopropoxycyclopropyl)-3-methyl-phenylethynyl]-benzoate  
12 (**Compound 83, General Formula 2**)

13 Using General Procedure F; 4-ethynyl-1-(1-isopropoxycyclopropyl)-3-  
14 methyl-benzene (**Intermediate 81**, 80.0 mg, 0.13 mmol) and ethyl-4-iodo  
15 benzoate (**Reagent A**, 100.0 mg, 0.36 mmol) in triethylamine (5 mL) was  
16 treated with copper(I)iodide (25.0 mg, 0.13 mmol) and sparged with argon for  
17 5 minutes. Dichlorobis(triphenylphosphine)-palladium(II) (91 mg, 0.13  
18 mmol) was added and the reaction mixture was stirred overnight at room  
19 temperature. Column chromatography (2-4% EtOAc - hexanes) afforded 75.0  
20 mg (56%) of the title compound as an orange solid.

21 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 8.02 (2H, d, J = 8.2 Hz), 7.57 (2H, d, J = 8.2 Hz), 7.39  
22 (1H, s), 7.29-7.20 (2H, m), 4.39 (2H, q, J = 7.1 Hz), 3.60 (1H, septet, J = 6.2  
23 Hz), 1.40 (3H, t, J = 7.1 Hz), 1.13 (2H, m), 0.97 (6H, d, J = 6.2 Hz), 0.87 (2H,  
24 m).

25 Methyl {4-[4-(1-isopropoxycyclopropyl)-3-methyl-phenylethynyl]-phenyl}-  
26 acetate (**Compound 84, General Formula 2**)

27 Using General Procedure F; 1-ethynyl-4-(1-isopropoxycyclopropyl)-3-  
28 methyl-benzene (**Intermediate 81**, 100.0 mg, 0.47 mmol) and methyl-(4-



1 iodophenyl)-acetate (**Reagent B**, 129.0 mg, 0.45 mmol) in triethylamine (6  
2 mL) was treated with copper(I)iodide (30.0 mg, 0.16 mmol) and sparged with  
3 argon for 5 minutes. Dichlorobis(triphenylphosphine)palladium(II) (110 mg,  
4 0.16 mmol) was added and the reaction mixture was stirred overnight at room  
5 temperature. Column chromatography (2-4% EtOAc - hexanes) afforded  
6 120.0 mg (71%) of the title compound.

7 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.48 (2H, d, J = 8.5 Hz), 7.36 (1H, s), 7.29-7.22 (4H, m),  
8 3.70 (3H, s), 3.63 (2H, s), 3.60 (1H, septet, J = 6.2 Hz), 2.52 (3H, s), 1.09 (2H,  
9 m), 0.97 (6H, d, J = 6.2 Hz), 0.86 (2H, m).

10 4-[4-(1-Isopropoxycyclopropyl)-3-methyl-phenylethynyl]-benzoic acid  
11 (**Compound 85, General Formula 2**)

12 Using General Procedure I; a solution of ethyl 4-[4-(1-  
13 isopropoxycyclopropyl)-3-methyl-phenylethynyl]-benzoate (**Compound 83**,  
14 60.0 mg, 0.17 mmol) in ethanol (2 mL) and tetrahydrofuran (2 mL) was  
15 treated with NaOH (80.0 mg, 2.0 mmols, 2.0 mL of a 1N aqueous solution)  
16 and stirred overnight at room temperature. Work-up afforded 38.0 mg (69%)  
17 of the title compound as a colorless solid.

18 <sup>1</sup>H NMR (d<sub>6</sub>-acetone) δ: 8.06 (2H, d, J = 8.5 Hz), 7.66 (2H, d, J = 8.5 Hz),  
19 7.42 (1H, s), 7.35 (2H, m), 3.59 (1H, septet, J = 6.2 Hz), 2.52 (3H, s), 1.07  
20 (2H, m), 0.93 (6H, d, J = 6.2 Hz), 0.88 (2H, m).

21 {4-[4-(1-Isopropoxycyclopropyl)-3-methyl-phenylethynyl]-phenyl}-acetic  
22 acid (**Compound 86, General Formula 2**)

23 Using General Procedure I; a solution of methyl {4-[4-(1-  
24 isopropoxycyclopropyl)-3-methyl-phenylethynyl]-phenyl}-acetate  
25 (**Compound 84**, 100.0 mg, 0.28 mmol) in ethanol (3 mL) and tetrahydrofuran  
26 (3 mL) was treated with NaOH (120.0 mg, 3.0 mmols, 3.0 mL of a 1N  
27 aqueous solution) and stirred overnight at room temperature. Work-up  
28 afforded 60.0 mg (62%) of the title compound as a colorless solid.

1 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.48 (2H, d, J = 7.6 Hz), 7.36 (1H, s), 7.25 (4H, m), 3.65  
2 (2H, s), 3.60 (1H, septet, J = 6.2 Hz), 2.51 (3H, s), 1.12 (2H, m), 0.97 (6H, d, J  
3 = 6.2 Hz), 0.86 (2H, m).

4 2,2-Dimethylpropyl 2-methyl-4-bromobenzoate (**Intermediate 82**)

5 Using General Esterification Method C; 2-methyl-4-bromo-benzoic  
6 acid (1.82 g, 8.47 mmols) was refluxed for 3h with 10 mL SOCl<sub>2</sub>. The  
7 resulting solution was concentrated under reduced pressure and the crude acyl  
8 chloride combined with 2,2-dimethylpropanol (0.75 g, 8.47 mmols) and  
9 pyridine (1.4 mL, 16.9 mmols) to give the title compound (1.64 g, 68%) after  
10 work-up and column chromatography (2-5% EtOAc - hexanes) as a colorless  
11 oil.

12 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.81 (1H, d, J = 8.2 Hz), 7.42 (1H, d, J = 2.0 Hz), 7.39  
13 (1H, dd, J = 2.0, 8.2 Hz), 3.99 (2H, s), 2.60 (3H, s), 1.03 (9H, s).

14 4-Bromo-1-[1-(2,2-dimethylpropyloxy)-vinyl]-2-methyl-benzene  
15 (**Intermediate 83**)

16 Using General Procedure 1; 2,2-dimethylpropyl 2-methyl-4-  
17 bromobenzoate (**Intermediate 82**, 820.0 mg, 2.87 mmols) and 5.8 mL of  
18 Tebbe's Reagent (817.0 mg, 2.87 mmols) afforded 800.0 mg (98%) of the title  
19 compound as a colorless oil after column chromatography (100% hexanes).

20 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.32 (1H, d, J = 2.0 Hz), 7.28 (1H, dd, J = 2.0, 8.2 Hz),  
21 7.18 (1H, d, J = 8.2 Hz), 4.27 (1H, d, J = 2.1 Hz), 4.10 (1H, d, J = 2.1 Hz),  
22 3.43 (2H, s), 2.33 (3H, s), 0.98 (9H, s).

23 4-Bromo-1-[1-(2,2-dimethylpropyloxy)-cyclopropyl]-2-methyl-benzene  
24 (**Intermediate 84**)

25 Using General Procedure 2; 4-bromo-1-[1-(2,2-dimethylpropyloxy)-  
26 cyclopropyl]-2-methyl-benzene (**Intermediate 83**, 400.0 mg, 1.43 mmols),  
27 Et<sub>2</sub>Zn (353.2 mg, 2.86 mmols), and CH<sub>2</sub>I<sub>2</sub> (760.0 mg, 2.86 mmols) in 3.0 mL  
28 Et<sub>2</sub>O afforded 370.0 mg (87%) of the title compound as a colorless oil after

1 chromatography (3% EtOAc - hexanes).

2 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.36 (1H, s), 7.27 (1H, d, J = 8.5 Hz), 7.09 (1H, d, J = 7.9  
3 Hz), 2.86 (2H, s), 2.52 (3H, s), 1.08 (2H, m), 0.83 (2H, m), 0.80 (9H, s).

4 [4-[1-[1-(2,2-Dimethylpropyloxy)-cyclopropyl]-3-methyl-phenylethynyl]]-  
5 trimethylsilane (Intermediate 84a)

6 Using General Procedure D; 4-bromo-1-[1-(2,2-dimethylpropyloxy)-  
7 cyclopropyl]-2-methyl-benzene (**Intermediate 84**, 255.0 mg, 0.86 mmol) in  
8 triethylamine (8 mL) was treated with copper(I)iodide (17.0 mg, 0.09 mmol)  
9 and then sparged with argon for 5 minutes. Trimethylsilylacetylene (0.70 g,  
10 7.1 mmols) was then added followed by dichlorobis-

11 (triphenylphosphine)palladium(II) (63.0 mg, 0.09 mmol). The resulting  
12 reaction mixture was heated to 70 °C for 5d. The title compound (220.0 mg,  
13 81%) was isolated by chromatography (1-2% EtOAc - hexanes).

14 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.30 (1H, s), 7.21 (1H, d, J = 7.6 Hz), 7.12 (1H, d, J = 8.6  
15 Hz), 2.80 (2H, s), 2.47 (3H, s), 1.05 (2H, m), 0.82 (2H, m), 0.75 (9H, s), 0.24  
16 (9H, s).

17 4-Ethynyl-1-[1-(2,2-dimethylpropyloxy)-cyclopropyl]-2-methyl-benzene  
18 (**Intermediate 85**)

19 Using General Procedure E; [4-[1-[1-(2,2-dimethylpropyloxy)-  
20 cyclopropyl]]-3-methyl-phenylethynyl]-trimethylsilane (**Intermediate 84a**,  
21 220.0 mg, 0.83 mmol) in methanol (10 mL) was treated with potassium  
22 carbonate (80.0 mg, 0.58 mmol) and stirred overnight at ambient temperature.  
23 The crude alkyne (155 mg, 76%) was used directly in the next reaction.

24 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.32 (1H, s), 7.24 (1H, d, J = 7.1 Hz), 7.15 (1H, d, J = 7.1  
25 Hz), 3.04 (1H, s), 2.83 (2H, s), 2.49 (3H, s), 1.06 (2H, m), 0.83 (2H, m), 0.76  
26 (9H, s).

27 Ethyl 4-[4-[1-(2,2-dimethylpropyloxy)-cyclopropyl]-3-methyl-phenylethynyl]-  
28 benzoate (Compound 87, General Formula 2)

1       Using General Procedure F; 4-ethynyl-1-[1-(2,2-dimethylpropyloxy)-  
2 cyclopropyl]-3-methyl-benzene (**Intermediate 85**, 75.0 mg, 0.31 mmol) and  
3 ethyl-4-iodo benzoate (**Reagent A**, 86.0 mg, 0.31 mmol) in triethylamine (5  
4 mL) was treated with copper(I)iodide (21.0 mg, 0.11 mmol) and sparged with  
5 argon for 5 minutes. Dichlorobis(triphenylphosphine)-palladium(II) (78 mg,  
6 0.11 mmol) was added and the reaction mixture was stirred overnight at room  
7 temperature. Column chromatography (2-4% EtOAc - hexanes) afforded 60.0  
8 mg (50%) of the title compound as an orange solid.

9 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 8.02 (2H, d, J = 8.4 Hz), 7.56 (2H, d, J = 8.4 Hz), 7.38  
10 (1H, s), 7.30 (1H, dd, J = 1.1, 8.0 Hz), 7.20 (1H, d, J = 8.0 Hz), 4.38 (2H, q, J  
11 = 7.1 Hz), 2.84 (2H, s), 2.52 (3H, s), 1.40 (3H, t, J = 7.1 Hz), 1.07 (2H, m),  
12 0.84 (2H, m), 0.77 (9H, s).

13 Methyl {4-[4-[1-(2,2-dimethylpropyloxy)-cyclopropyl]-3-methyl-  
14 phenylethynyl]-phenyl}-acetate (**Compound 88, General Formula 2**)

15       Using General Procedure F; 4-ethynyl-1-[1-(2,2-dimethylpropyloxy)-  
16 cyclopropyl]-3-methyl-benzene (**Intermediate 85**, 75.0 mg, 0.31 mmol) and  
17 methyl-(4-iodophenyl)-acetate (**Reagent B**, 86.0 mg, 0.31 mmol) in  
18 triethylamine (6 mL) was treated with copper(I)iodide (21.0 mg, 0.11 mmol)  
19 and sparged with argon for 5 minutes.  
20 Dichlorobis(triphenylphosphine)palladium(II) (78 mg, 0.11 mmol) was added  
21 and the reaction mixture was stirred overnight at room temperature. Column  
22 chromatography (2-4% EtOAc - hexanes) afforded 100.0 mg (83%) of the title  
23 compound.

24 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.48 (2H, d, J = 7.9 Hz), 7.36-7.24 (4H, m), 7.18 (1H, d, J  
25 = 7.9 Hz), 3.70 (3H, s), 3.63 (2H, s), 2.84 (2H, s), 2.51 (3H, s), 1.07 (2H, m),  
26 0.83 (2H, m), 0.77 (9H, s).

27 4-[4-[1-(2,2-Dimethylpropyloxy)-cyclopropyl]-3-methyl-phenylethynyl]-  
28 benzoic acid (**Compound 89, General Formula 2**)

1        Using General Procedure I; a solution of ethyl 4-[4-[1-(2,2-  
2 dimethylpropyloxy)-cyclopropyl]-3-methyl-phenylethynyl]-benzoate  
3 (**Compound 87**, 60.0 mg, 0.15 mmol) in ethanol (3 mL) and tetrahydrofuran  
4 (3 mL) was treated with NaOH (120.0 mg, 3.0 mmols, 3.0 mL of a 1N  
5 aqueous solution) and stirred overnight at room temperature. Work-up  
6 afforded 24.0 mg (43%) of the title compound as a colorless solid.  
7 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 8.06 (2H, d, J = 7.9 Hz), 7.65 (2H, d, J = 7.9 Hz), 7.42  
8 (1H, s), 7.33 (2H, m), 2.89 (2H, s), 2.53 (3H, s), 1.07 (2H, m), 0.90 (2H, m),  
9 0.77 (9H, s).

10 {4-[4-[1-(2,2-Dimethylpropyloxy)-cyclopropyl]-3-methyl-phenylethynyl]-  
11 phenyl}-acetic acid (**Compound 90**, General Formula 2)

12        Using General Procedure I; a solution of methyl {4-[4-[1-(2,2-  
13 dimethylpropyloxy)-cyclopropyl]-3-methyl-phenylethynyl]-phenyl}-acetate  
14 (**Compound 88**, 95.0 mg, 0.24 mmol) in ethanol (3 mL) and tetrahydrofuran  
15 (3 mL) was treated with NaOH (120.0 mg, 3.0 mmols, 3.0 mL of a 1N  
16 aqueous solution) and stirred overnight at room temperature. Work-up  
17 afforded 49.0 mg (53%) of the title compound as a colorless solid.  
18 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.49 (2H, d, J = 8.2 Hz), 7.36 (1H, s), 7.27 (3H, m), 7.18  
19 (1H, d, J = 7.9 Hz), 3.66 (2H, s), 2.84 (2H, s), 2.51 (3H, s), 1.07 (2H, m), 0.83  
20 (2H, m), 0.77 (9H, s).

21 Benzyl 4-bromo-2-ethyl-benzoate (**Intermediate 86**)

22        Using General Esterification Method B; 4-bromo-2-ethyl-benzoic acid  
23 (0.98 g, 4.25 mmols), benzyl bromide (0.80 g, 4.68 mmols), and K<sub>2</sub>CO<sub>3</sub> (0.64  
24 g, 4.68 mmols) afforded 1.0 g (74%) of the title compound after column  
25 chromatography (0-3% EtOAc - hexanes).

26 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.76 (1H, d, J = 8.5 Hz), 7.41-7.33 (7H, m), 5.32 (2H, s),  
27 2.95 (2H, q, J = 7.6 Hz), 1.20 (3H, t, J = 7.6 Hz).

28 4-Bromo-1-(1-benzyloxyvinyl)-2-ethyl-benzene (**Intermediate 87**)

1       Using General Procedure 1; benzyl 4-bromo-2-ethylbenzoate  
2 (Intermediate 86, 1.20 g, 3.78 mmols) and 7.6 mL of Tebbe's Reagent (1.08  
3 g, 3.78 mmols) afforded 800.0 mg (66%) of the title compound after column  
4 chromatography (100% hexanes).

5 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.37-7.17 (8H, m), 4.88 (2H, s), 4.43 (1H, d, J = 2.1 Hz),  
6 4.25 (1H, d, J = 2.1 Hz), 2.71 (2H, q, J = 7.6 Hz), 1.18 (3H, t, J = 7.6 Hz).

7 4-Bromo-1-(1-benzyloxycyclopropyl)-2-ethyl-benzene (Intermediate 88)

8       Using General Procedure 2; 4-bromo-1-(1-benzyloxyvinyl)-2-ethyl-  
9 benzene (Intermediate 87, 330.0 mg, 1.04 mmols), Et<sub>2</sub>Zn (257.0 mg, 2.08  
10 mmols), and CH<sub>2</sub>I<sub>2</sub> (557.0 mg, 2.08 mmols) in 4 mL Et<sub>2</sub>O afforded 241.0 mg  
11 (70%) of the title compound as a colorless oil after chromatography (2-5%  
12 EtOAc - hexanes).

13 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.43-7.15 (8H, m), 4.27 (2H, s), 3.00 (2H, q, J = 7.6 Hz),  
14 1.29-1.21 (5H, m), 0.90 (2H, m).

15 [4-(1-Benzyloxycyclopropyl)-3-ethyl-phenylethynyl]-trimethylsilane  
16 (Intermediate 89)

17       Using General Procedure D; 4-bromo-1-(1-benzyloxycyclopropyl)-2-  
18 ethyl-benzene (Intermediate 88, 220.0 mg, 0.66 mmol) in triethylamine (8  
19 mL) was treated with copper(I)iodide (14.0 mg, 0.07 mmol) and then sparged  
20 with argon for 5 minutes. Trimethylsilylacetylene (0.70 g, 7.1 mmols) was  
21 then added followed by dichlorobis-(triphenylphosphine)palladium(II) (50.0  
22 mg, 0.07 mmol). The resulting reaction mixture was heated to 70 °C for 5d.  
23 The title compound was isolated by chromatography (0 - 2% EtOAc -  
24 hexanes).

25 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.41-7.13 (8H, m), 4.24 (2H, s), 2.98 (2H, q, J = 7.6 Hz),  
26 1.25 (3H, t, J = 7.6 Hz), 1.20 (2H, m), 0.90 (2H, m), 0.26 (9H, s).

27 4-Ethynyl-1-(1-benzyloxycyclopropyl)-2-ethyl-benzene (Intermediate 90)

28       Using General Procedure E; [4-(1-benzyloxycyclopropyl)-3-ethyl-

1 phenylethynyl]-trimethylsilane (**Intermediate 89**, 240 mg, 0.69 mmol) in  
2 methanol (6 mL) was treated with potassium carbonate (10.0 mg, 0.72 mmol)  
3 and stirred overnight at ambient temperature. The crude alkyne (190 mg,  
4 99%) was used directly in the next reaction. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.43-7.15  
5 (8H, m), 4.27 (2H, s), 3.08 (1H, s), 3.01 (2H, q, J = 7.6 Hz), 1.26 (3H, t, J =  
6 7.6 Hz), 1.22 (2H, m), 0.92 (2H, m).

7 Ethyl 4-[4-(1-benzyloxycyclopropyl)-3-ethyl-phenylethynyl]-benzoate  
8 (**Compound 91, General Formula 2**)

9 Using General Procedure F; 1-ethynyl-4-(1-benzyloxycyclopropyl)-3-  
10 ethyl-benzene (**Intermediate 90**, 90.0 mg, 0.33 mmol) and ethyl-4-iodo  
11 benzoate (**Reagent A**, 100.0 mg, 0.36 mmol) in triethylamine (5 mL) was  
12 treated with copper(I)iodide (21.0 mg, 0.11 mmol) and sparged with argon for  
13 5 minutes. Dichlorobis(triphenylphosphine)palladium(II) (77 mg, 0.11 mmol)  
14 was added and the reaction mixture was stirred overnight at room temperature.  
15 Column chromatography (2-4% EtOAc - hexanes) afforded 100.0 mg (72%)  
16 of the title compound.

17 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 8.03 (2H, d, J = 7.9 Hz), 7.59 (2H, d, J = 7.9 Hz), 7.49  
18 (1H, s), 7.36-7.16 (7H, m), 4.38 (2H, q, J = 7.1 Hz), 4.28 (2H, s), 3.04 (2H, q,  
19 J = 7.6 Hz), 1.40 (3H, t, J = 7.1 Hz), 1.29 (3H, t, J = 7.6 Hz), 1.23 (2H, m),  
20 0.94 (2H, m).

21 Methyl {4-[4-(1-benzyloxycyclopropyl)-3-ethyl-phenylethynyl]-phenyl}-  
22 acetate (**Compound 92, General Formula 2**)

23 Using General Procedure F; 1-ethynyl-4-(1-benzyloxycyclopropyl)-3-  
24 ethyl-benzene (**Intermediate 90**, 107.0 mg, 0.39 mmol) and methyl-(4-  
25 iodophenyl)-acetate (**Reagent B**, 110.0 mg, 0.39 mmol) in triethylamine (5  
26 mL) was treated with copper(I)iodide (25.0 mg, 0.13 mmol) and sparged with  
27 argon for 5 minutes. Dichlorobis(triphenylphosphine)palladium(II) (91 mg,  
28 0.13 mmol) was added and the reaction mixture was stirred overnight at room

1 temperature. Column chromatography (2-4% EtOAc - hexanes) afforded  
2 130.0 mg (79%) of the title compound as a pale-yellow oil.  
3 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.49 (3H, m), 7.32-7.16 (9H, m), 4.28 (2H, s), 3.71 (3H,  
4 s), 3.64 (2H, s), 3.03 (2H, q, J = 7.6 Hz), 1.32-1.23 (5H, m), 0.94 (2H, m).

5 4-[4-(1-Benzyloxycyclopropyl)-3-ethyl-phenylethynyl]-benzoic acid

6 **(Compound 93, General Formula 2)**

7 Using General Procedure I; a solution of ethyl 4-[4-(1-  
8 benzyloxycyclopropyl)-3-ethyl-phenylethynyl]-benzoate (**Compound 91**,  
9 100.0 mg, 0.24 mmol) in ethanol (3 mL) and tetrahydrofuran (3 mL) was  
10 treated with NaOH (120.0 mg, 3.0 mmols, 3.0 mL of a 1N aqueous solution)  
11 and stirred overnight at room temperature. Work-up and purification by  
12 HPLC (Partisil 10-pac, 10% H<sub>2</sub>O/CH<sub>3</sub>CN) afforded the title compound as a  
13 colorless solid.

14 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 8.10 (2H, d, J = 8.5 Hz), 7.64 (2H, d, J = 8.5 Hz), 7.50  
15 (1H, s), 7.35-7.16 (7H, m), 4.29 (2H, s), 3.04 (2H, q, J = 7.6 Hz), 1.30 (3H, t, J  
16 = 7.6 Hz), 1.25 (2H, m), 0.95 (2H, m).

17 {4-[4-(1-Benzyloxycyclopropyl)-3-ethyl-phenylethynyl]-phenyl}-acetic acid

18 **(Compound 94, General Formula 2)**

19 Using General Procedure I; a solution of methyl {4-[4-(1-  
20 benzyloxycyclopropyl)-3-ethyl-phenylethynyl]-phenyl}-acetate (**Compound**  
21 **92**, 130.0 mg, 0.31 mmol) in ethanol (3 mL) and tetrahydrofuran (3 mL) was  
22 treated with NaOH (120.0 mg, 3.0 mmols, 3.0 mL of a 1N aqueous solution)  
23 and stirred overnight at room temperature. Work-up and purification by  
24 HPLC (Partisil 10-pac, 10% H<sub>2</sub>O/CH<sub>3</sub>CN) afforded the title compound.

25 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.49 (3H, m), 7.31-7.16 (9H, m), 4.28 (2H, s), 3.66 (2H,  
26 s), 3.02 (2H, q, J = 7.6 Hz), 1.29 (3H, t, J = 7.6 Hz), 1.23 (2H, m), 0.94 (2H,  
27 m).

28 Isopropyl 2-ethyl-4-bromobenzoate (**Intermediate 91**)



1       Using General Esterification Procedure A; 4-bromo-2-ethyl-benzoic  
2 acid (2.25 g, 9.9 mmols) was combined with isopropyl alcohol to give the title  
3 compound as a colorless oil after column chromatography (2% EtOAc-  
4 hexanes).

5  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 7.69 (1H, d,  $J = 8.5$  Hz), 7.41 (1H, s), 7.36 (1H, d,  $J = 8.5$   
6 Hz), 5.23 (1H, septet,  $J = 6.2$  Hz), 2.95 (2H, q,  $J = 7.6$  Hz), 1.37 (6H, d,  $J = 6.2$   
7 Hz), 1.23 (3H, t,  $J = 7.6$  Hz).

8 4-Bromo-1-(1-isopropoxyvinyl)-2-ethyl-benzene (Intermediate 92)

9       Using General Procedure 1; isopropyl 2-ethyl-4-bromobenzoate  
10 (**Intermediate 91**, 1.21 g, 4.46 mmols) and 8.9 mL of Tebbe's Reagent (1.27  
11 g, 4.46 mmols) afforded 570.0 mg (75%) of the title compound after column  
12 chromatography (100% hexanes).

13  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 7.36 (1H, d,  $J = 2.0$  Hz), 7.28 (1H, dd,  $J = 2.0, 8.0$  Hz),  
14 7.17 (1H, d,  $J = 8.0$  Hz), 4.39 (1H, septet,  $J = 6.2$  Hz), 4.31 (1H, d,  $J = 2.1$  Hz),  
15 4.26 (1H, d,  $J = 2.1$  Hz), 2.73 (2H, q,  $J = 7.6$  Hz), 1.35 (6H, d,  $J = 6.2$  Hz),  
16 1.24 (3H, t,  $J = 7.6$  Hz).

17 4-Bromo-1-(1-isopropoxycyclopropyl)-2-ethyl-benzene (Intermediate 93)

18       Using General Procedure 2; 4-bromo-1-(1-isopropoxyvinyl)-2-ethyl-  
19 benzene (**Intermediate 92**, 570.0 mg, 2.11 mmols),  $\text{Et}_2\text{Zn}$  (521.0 mg, 4.22  
20 mmols), and  $\text{CH}_2\text{I}_2$  (1.13 g, 4.22 mmols) in 7.0 mL  $\text{Et}_2\text{O}$  afforded 500.0 mg  
21 (85%) of the title compound as a colorless oil after chromatography (3%  
22 EtOAc - hexanes).

23  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 7.39 (1H, d,  $J = 2.1$  Hz), 7.25 (1H, dd,  $J = 2.1, 8.1$  Hz),  
24 7.15 (1H, d,  $J = 8.1$  Hz), 3.59 (1H, septet,  $J = 6.2$  Hz), 2.97 (2H, q,  $J = 7.6$  Hz),  
25 1.27 (3H, t,  $J = 7.6$  Hz), 1.11 (2H, m), 0.97 (6H, d,  $J = 6.2$  Hz), 0.83 (2H, m).

26 [4-(1-Isopropoxycyclopropyl)-3-ethyl-phenylethynyl]-trimethylsilane  
27 (**Intermediate 94**)

28       Using General Procedure D; 4-bromo-1-(1-isopropoxycyclopropyl)-2-

1 ethyl-benzene (**Intermediate 93**, 300.0 mg, 1.07 mmol) in triethylamine (8  
2 mL) was treated with copper(I)iodide (20.0 mg, 0.11 mmol) and then sparged  
3 with argon for 5 minutes. Trimethylsilylacetylene (0.70 g, 7.1 mmols) was  
4 then added followed by dichlorobis-(triphenylphosphine)palladium(II) (75.0  
5 mg, 0.11 mmol). The resulting reaction mixture was heated to 70 °C for 5d.  
6 The title compound (320.0 mg, 99%) was isolated by chromatography (0 - 2%  
7 EtOAc - hexanes) as an orange oil.  
8 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.37-7.21 (3H, m), 3.56 (1H, septet, J = 6.2 Hz), 2.96  
9 (2H, q, J = 7.6 Hz), 1.27 (3H, t, J = 7.6 Hz), 1.10 (2H, m), 0.94 (6H, d, J = 6.2  
10 Hz), 0.84 (2H, m), 0.25 (9H, s).

11 4-Ethynyl-1-(1-isopropoxycyclopropyl)-2-ethyl-benzene (**Intermediate 95**)

12 Using General Procedure E; [4-(1-isopropoxycyclopropyl)-3-ethyl-  
13 phenylethynyl]-trimethylsilane (**Intermediate 94**, 330.0 mg, 1.10 mmols) in  
14 methanol (10 mL) was treated with potassium carbonate (150.0 mg, 1.10  
15 mmol) and stirred overnight at ambient temperature. The crude alkyne (238  
16 mg, 95%) was used directly in the next reaction.

17 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.40-7.22 (3H, m), 3.59 (1H, septet, J = 6.2 Hz), 3.07  
18 (1H, s), 2.97 (2H, q, J = 7.6 Hz), 1.28 (3H, t, J = 7.6 Hz), 1.12 (2H, m), 0.96  
19 (6H, d, J = 6.2 Hz), 0.85 (2H, m).

20 Ethyl 4-[4-(1-isopropoxycyclopropyl)-3-ethyl-phenylethynyl]-benzoate

21 (**Compound 95, General Formula 2**)

22 Using General Procedure F; 4-ethynyl-1-(1-isopropoxycyclopropyl)-3-  
23 ethyl-benzene (**Intermediate 95**, 108.0 mg, 0.47 mmol) and ethyl-4-iodo  
24 benzoate (**Reagent A**, 130.0 mg, 0.47 mmol) in triethylamine (5 mL) was  
25 treated with copper(I)iodide (30.0 mg, 0.16 mmol) and sparged with argon for  
26 5 minutes. Dichlorobis(triphenylphosphine)-palladium(II) (110 mg, 0.16  
27 mmol) was added and the reaction mixture was stirred overnight at room  
28 temperature. Column chromatography (2-4% EtOAc - hexanes) afforded

1 125.0 mg (71%) of the title compound as an oil.

2 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 8.02 (2H, d, J = 8.2 Hz), 7.59 (2H, d, J = 8.2 Hz), 7.46  
3 (1H, s), 7.33-7.26 (2H, m), 4.39 (2H, q, J = 7.1 Hz), 3.62 (1H, septet, J = 6.2  
4 Hz), 3.01 (2H, q, J = 7.6 Hz), 1.41 (3H, t, J = 7.1 Hz), 1.31 (3H, t, J = 7.1 Hz),  
5 1.14 (2H, m), 0.97 (6H, d, J = 6.2 Hz), 0.88 (2H, m).

6 Methyl {4-[4-(1-isopropoxycyclopropyl)-3-ethyl-phenylethynyl]-phenyl}-  
7 acetate (Compound 96, General Formula 2)

8 Using General Procedure F; 1-ethynyl-4-(1-isopropoxycyclopropyl)-3-  
9 ethyl-benzene (**Intermediate 95**, 130.0 mg, 0.57 mmol) and methyl-(4-  
10 iodophenyl)-acetate (**Reagent B**, 157.0 mg, 0.57 mmol) in triethylamine (5  
11 mL) was treated with copper(I)iodide (36.0 mg, 0.19 mmol) and sparged with  
12 argon for 5 minutes. Dichlorobis(triphenylphosphine)palladium(II) (133 mg,  
13 0.19 mmol) was added and the reaction mixture was stirred overnight at room  
14 temperature. Column chromatography (2-5% EtOAc - hexanes) afforded  
15 150.0 mg (70%) of the title compound as an orange oil.

16 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.50-7.44 (3H, m), 7.27 (4H, m), 3.70 (3H, s), 3.64 (2H,  
17 s), 3.62 (1H, septet, J = 6.2 Hz), 3.00 (2H, q, J = 7.6 Hz), 1.30 (3H, t, J = 7.6  
18 Hz), 1.13 (2H, m), 0.97 (6H, d, J = 6.2 Hz), 0.87 (2H, m).

19 4-[4-(1-Isopropoxycyclopropyl)-3-ethyl-phenylethynyl]-benzoic acid  
20 (Compound 97, General Formula 2)

21 Using General Procedure I; a solution of ethyl 4-[4-(1-  
22 isopropoxycyclopropyl)-3-ethyl-phenylethynyl]-benzoate (**Compound 95**,  
23 110.0 mg, 0.29 mmol) in ethanol (3 mL) and tetrahydrofuran (3 mL) was  
24 treated with NaOH (120.0 mg, 3.0 mmols, 3.0 mL of a 1N aqueous solution)  
25 and stirred overnight at room temperature. Work-up and isolation by HPLC  
26 (partisil 10-pac, 10% H<sub>2</sub>O/CH<sub>3</sub>CN) afforded the title compound as a colorless  
27 solid.

28 <sup>1</sup>H NMR (d<sub>6</sub>-acetone) δ: 8.06 (2H, d, J = 8.2 Hz), 7.67 (2H, d, J = 8.2 Hz),

1 7.49 (1H, s), 7.40-7.34 (2H, m), 3.61 (1H, septet, J = 6.2 Hz), 3.01 (2H, q, J =  
2 7.6 Hz), 1.29 (3H, t, J = 7.6 Hz), 1.08 (2H, m), 0.93 (6H, d, J = 6.2 Hz), 0.88  
3 (2H, m).

4 {4-[4-(1-Isopropoxycyclopropyl)-3-ethyl-phenylethynyl]-phenyl}-acetic acid  
5 **(Compound 98, General Formula 2)**

6 Using General Procedure I; a solution of methyl {4-[4-(1-  
7 isopropoxycyclopropyl)-3-ethyl-phenylethynyl]-phenyl}-acetate (**Compound**  
8 **96**, 156.0 mg, 0.41 mmol) in ethanol (3 mL) and tetrahydrofuran (3 mL) was  
9 treated with NaOH (120.0 mg, 3.0 mmols, 3.0 mL of a 1N aqueous solution)  
10 and stirred overnight at room temperature. Work-up and isolation by HPLC  
11 (partisil 10-pac, 10% H<sub>2</sub>O/CH<sub>3</sub>CN) afforded 85.0 mg (57%) of the title  
12 compound.

13 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.54-7.48 (3H, m), 7.34-7.27 (4H, m), 3.68 (2H, s), 3.66  
14 (1H, septet, J = 6.2 Hz), 3.03 (2H, q, J = 7.6 Hz), 1.33 (2H, t, J = 7.6 Hz), 1.17  
15 (2H, m), 1.01 (6H, d, J = 6.2 Hz), 0.90 (2H, m).

16 (4-Bromo-3-isopropyl-phenoxy)-triisopropyl-silane (Intermediate 96)

17 To a solution of 4-bromo-3-isopropylphenol (880.0 mg, 4.09 mmols)  
18 and imidazole (417.0 mg, 6.13 mmols) in 10 mL DMF was added chloro-  
19 triisopropylsilane (946.0 mg, 4.90 mmols). After stirring overnight at room  
20 temperature the solution was diluted with H<sub>2</sub>O and extracted with EtOAc. The  
21 combined organic layers were washed with H<sub>2</sub>O and saturated aqueous NaCl  
22 before being dried (MgSO<sub>4</sub>) and concentrated under reduced pressure. The  
23 title compound, 1.30 g (92%), was isolated by column chromatography (1-2%  
24 EtOAc-hexanes) as a colorless oil.

25 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.34 (1H, d, J = 8.5 Hz), 6.81 (1H, d, J = 2.9 Hz), 6.59  
26 (1H, dd, J = 2.9, 8.5 Hz), 3.31 (1H, septet, J = 7.0 Hz), 1.33-1.21 (3H, m), 1.24  
27 (6H, d, J = 7.0 Hz), 1.13 (18H, d, J = 7.0 Hz).

28 Ethyl 2-isopropyl-4-triisopropylsilanyloxy-benzoate (Intermediate 97)

1 To a solution of (4-bromo-3-isopropyl-phenoxy)-triisopropyl-silane  
2 (**Intermediate 96**, 1.3 g, 3.8 mmols) in 15 mL Et<sub>2</sub>O cooled to -78 °C was  
3 added 4.9 mL of *tert*-butyllithium in pentane (532.0 mg, 8.3 mmols; 1.7 M).  
4 After stirring for 30 minutes ethyl chloroformate (832.0 mg, 7.8 mmols) was  
5 added. The resulting solution was warmed to room temperature and quenched  
6 by the addition of saturated aqueous NH<sub>4</sub>Cl. The mixture was extracted with  
7 EtOAc and the combined organic layers dried (MgSO<sub>4</sub>) concentrated under  
8 reduced pressure and the residue chromatographed (4% EtOAc-hexanes) to  
9 give 1.09 g (85%) of the title compound as a colorless oil.

10 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.72 (1H, d, J = 8.5 Hz), 6.87 (1H, d, J = 2.3 Hz), 6.69  
11 (1H, dd, J = 2.3, 8.5 Hz), 3.88 (1H, septet; J = 7.1 Hz), 4.30 (2H, q, J = 7.1  
12 Hz), 1.36 (3H, t, J = 7.1 Hz), 1.31-1.17 (9H, m), 1.09 (18H).

13 [4-(1-Ethoxyvinyl)-3-isopropyl-phenoxy]-triisopropyl-silane (**Intermediate**  
14 **98**)

15 Using General Procedure 1; ethyl 2-isopropyl-4-triisopropylsilanyloxy-  
16 benzoate (**Intermediate 97**, 450.0 mg, 1.34 mmols) and 2.0 mL of Tebbe's  
17 Reagent (398.0 mg, 1.40 mmols) afforded the title compound after column  
18 chromatography (100% hexanes).

19 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.11 (1H, d, J = 8.2 Hz), 6.78 (1H, d, J = 2.3 Hz), 6.63  
20 (1H, dd, J = 2.3, 8.2 Hz), 4.23 (1H, d, J = 1.7 Hz), 4.10 (1H, d, J = 1.7 Hz),  
21 3.86 (2H, q, J = 7.0 Hz), 3.16 (1H, septet, J = 7.0 Hz), 1.35 (3H, t, J = 7.1 Hz),  
22 1.28-1.19 (3H, m), 1.19 (6H, d, J = 7.0 Hz), 1.11 (18H).

23 [4-(1-Ethoxycyclopropyl)-3-isopropyl-phenoxy]-triisopropyl-silane  
24 (**Intermediate 99**)

25 Using General Procedure 2; [4-(1-ethoxyvinyl)-3-isopropyl-phenoxy]-  
26 triisopropyl-silane (**Intermediate 98**, 300.0 mg, 0.83 mmols), Et<sub>2</sub>Zn (325.0  
27 mg, 2.63 mmols), and CH<sub>2</sub>I<sub>2</sub> (704.0 mg, 2.63 mmols) in 5.0 mL Et<sub>2</sub>O afforded  
28 270.0 mg (86%) of the title compound as a colorless oil after chromatography

1 (0.5-2.5% EtOAc - hexanes).

2 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.06 (1H, d, J = 8.2 Hz), 6.81 (1H, d, J = 2.6 Hz), 6.59  
3 (1H, dd, J = 2.6, 8.2 Hz), 3.76 (1H, septet, J = 7.0 Hz), 3.25 (2H, q, J = 7.0  
4 Hz), 1.30-1.20 (3H, m), 1.19 (6H, d, J = 7.0 Hz), 1.15 (2H, m), 1.10 (18H),  
5 1.02 (2H, t, J = 7.0 Hz), 0.82 (2H, m).

6 4-(1-Ethoxycyclopropyl)-3-isopropyl-phenol (**Intermediate 100**)

7 To a solution of [4-(1-ethoxycyclopropyl)-3-isopropyl-phenoxy]-  
8 triisopropyl-silane (**Intermediate 99**, 360.0 mg, 0.96mmol) in 3 mL THF at 0  
9 °C was added tetrabutylammonium fluoride (625.0 mg, 2.39 mmols, 2.4 mL of  
10 a 1 M solution in THF). The solution was stirred at 0 °C for 30 minutes and  
11 then quenched by the addition of H<sub>2</sub>O. The mixture was extracted with EtOAc  
12 and the combined organic layers were washed with H<sub>2</sub>O and saturated aqueous  
13 NaCl before being dried (MgSO<sub>4</sub>) and concentrated under reduced pressure.  
14 The title compound (180 mg, 86%) was isolated from the residue by column  
15 chromatography (4-10% EtOAc-hexanes) as a colorless solid.

16 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.13 (1H, d, J = 8.2 Hz), 6.79 (1H, d, J = 2.6 Hz), 6.57  
17 (1H, dd, J = 2.6, 8.2 Hz), 5.48 (1H, s), 3.79 (1H, septet, J = 7.0 Hz), 3.32 (2H,  
18 q, J = 7.0 Hz), 1.21 (6H, d, J = 7.0 Hz), 1.12 (2H, m), 1.05 (3H, t, J = 7.0 Hz),  
19 0.84 (2H, m).

20 4-(1-Ethoxycyclopropyl)-3-isopropyl-phenyl 1,1,1-trifluoromethanesulfonate  
21 (**Intermediate 101**)

22 A solution of 4-(1-ethoxycyclopropyl)-3-isopropyl-phenol  
23 (**Intermediate 100**, 172.0 mg, 0.78 mmol) in 5 mL of CH<sub>2</sub>Cl<sub>2</sub> was cooled to 0  
24 °C and to it was added 2-[N,N-bis(trifluoromethylsulfonyl)amino]-5-  
25 chloropyridine (321.0 mg, 0.82 mmol) and triethylamine (240.0 mg, 2.4  
26 mmols). The resulting solution was warmed to room temperature and stirred  
27 overnight. The reaction was quenched by the addition of H<sub>2</sub>O and the mixture  
28 extracted with EtOAc and the combined organic layers were washed with 10%

1 aqueous HCl, saturated aqueous NaHCO<sub>3</sub>, H<sub>2</sub>O, and saturated aqueous NaCl.  
2 The solution was dried (MgSO<sub>4</sub>) and concentrated under reduced pressure.  
3 The title compound was isolated by column chromatography (2-4% EtOAc-  
4 hexanes) as a colorless oil, 240.0 mg, 87%.  
5 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.31 (1H, d, J = 8.6 Hz), 7.18 (1H, d, J = 2.6 Hz), 7.00  
6 (1H, dd, J = 2.6, 8.6 Hz), 3.87 (1H, septet, J = 7.0 Hz), 2.38 (2H, q, J = 7.0  
7 Hz), 1.24 (6H, d, J = 7.0 Hz), 1.15 (2H, m), 1.04 (3H, t, J = 7.0 Hz), 0.86 (2H,  
8 m).

9 [4-(1-Ethoxycyclopropyl)-3-isopropyl-phenylethynyl]-trimethylsilane  
10 **(Intermediate 102)**

11 Using General Procedure D; 4-(1-ethoxycyclopropyl)-3-isopropyl-  
12 phenyl 1,1,1-trifluoromethanesulfonate (**Intermediate 101**, 240.0 mg, 0.68  
13 mmol) in triethylamine (2 mL) and DMF (6 mL) was sparged with argon for 5  
14 minutes. Trimethylsilylacetylene (0.70 g, 7.1 mmols) was then added  
15 followed by dichlorobis-(triphenylphosphine)palladium(II) (38.0 mg, 0.05  
16 mmol). The resulting reaction mixture was heated to 95 °C for 5d. The title  
17 compound, 200.0 mg (99%), was isolated by chromatography (0 - 2% EtOAc -  
18 hexanes) as an orange oil.

19 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.43 (1H, d, J = 1.7 Hz), 7.25 (1H, dd, J = 1.7, 7.9 Hz),  
20 7.16 (1H, d, J = 7.9 Hz), 3.80 (1H, septet, J = 6.8 Hz), 3.26 (2H, q, J = 7.0 Hz),  
21 1.24 (6H, d, J = 6.8 Hz), 1.24-1.10 (2H, m), 1.03 (3H, t, J = 7.0 Hz), 0.87 (2H,  
22 s), 0.26 (9H, s).

23 1-(1-Ethoxycyclopropyl)-4-ethynyl-2-isopropylbenzene (**Intermediate 103**)

24 Using General Procedure E; [4-(1-ethoxycyclopropyl)-3-isopropyl-  
25 phenylethynyl]-trimethylsilane (**Intermediate 102**, 210.0 mg, 0.70 mmol) in  
26 methanol (10 mL) was treated with potassium carbonate (100.0 mg, 0.72  
27 mmol) and stirred overnight at ambient temperature. The crude alkyne was  
28 used directly in the next reaction.

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.47 (1H, d, J = 1.7 Hz), 7.23 (1H, dd, J = 1.7, 7.6 Hz),  
7.19 (1H, d, J = 7.6 Hz), 3.80 (1H, septet, J = 7.0 Hz), 3.27 (1H, q, J = 7.0 Hz),  
3.07 (1H, s), 1.23 (6H, d, J = 7.0 Hz), 1.13 (2H, m), 1.03 (3H, t, J = 7.0 Hz),  
0.85 (2H, m).

Ethyl 4-[4-(1-ethoxycyclopropyl)-3-isopropyl-phenylethynyl]-benzoate

**(Compound 99, General Formula 2)**

Using General Procedure F; 1-(1-ethoxycyclopropyl)-4-ethynyl-2-isopropylbenzene (**Intermediate 103**, 50.0 mg, 0.22 mmol) and ethyl-4-iodobenzoate (**Reagent A**, 60.0 mg, 0.22 mmol) in triethylamine (5 mL) was treated with copper(I)iodide (14.0 mg, 0.07 mmol) and sparged with argon for 5 minutes. Dichlorobis(triphenylphosphine)-palladium(II) (51 mg, 0.07 mmol) was added and the reaction mixture was stirred overnight at room temperature. Column chromatography (1-2% EtOAc - hexanes) afforded 28.0 mg (34%) of the title compound.

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 8.01 (2H, d, J = 8.2 Hz), 7.59 (2H, d, J = 8.2 Hz), 7.51 (1H, d, J = 1.7 Hz), 7.28 (1H, dd, J = 1.7, 7.9 Hz), 7.21 (1H, d, J = 7.9 Hz), 4.38 (2H, q, J = 7.1 Hz), 3.83 (1H, septet, J = 6.7 Hz), 3.29 (2H, q, J = 7.0 Hz), 1.40 (3H, t, J = 7.1 Hz), 1.26 (6H, d, J = 6.7 Hz), 1.14 (2H, m), 1.04 (3H, t, J = 7.0 Hz), 0.87 (2H, m).

Methyl {4-[4-(1-ethoxycyclopropyl)-3-isopropyl-phenylethynyl]-phenyl}-

acetate (Compound 100, General Formula 2)

Using General Procedure F; 1-(1-ethoxycyclopropyl)-4-ethynyl-2-isopropylbenzene (**Intermediate 103**, 120.0 mg, 0.52 mmol) and methyl-(4-iodophenyl)-acetate (**Reagent B**, 150.0 mg, 0.52 mmol) in triethylamine (8 mL) was treated with copper(I)iodide (32.0 mg, 0.17 mmol) and sparged with argon for 5 minutes. Dichlorobis(triphenylphosphine)palladium(II) (121 mg, 0.17 mmol) was added and the reaction mixture was stirred overnight at room temperature. Column chromatography (2-5% EtOAc - hexanes) afforded



1 140.0 mg (71%) of the title compound as a pale-yellow oil.

2 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.53 (3H, m), 7.31-7.23 (4H, m), 3.86 (1H, septet, J = 6.7  
3 Hz), 3.73 (3H, s), 3.67 (2H, s), 3.33 (2H, q, J = 7.0 Hz), 1.30 (6H, d, J = 6.7  
4 Hz), 1.15 (2H, m), 1.08 (3H, t, J = 7.0 Hz), 0.90 (2H, m).

5 4-[4-(1-Ethoxycyclopropyl)-3-isopropyl-phenylethynyl]-benzoic acid

6 **(Compound 101, General Formula 2)**

7 Using General Procedure I; A solution of ethyl 4-[4-(1-  
8 ethoxycyclopropyl)-3-isopropyl-phenylethynyl]-benzoate (**Compound 99**,  
9 28.0 mg, 0.07 mmol) in ethanol (2 mL) and tetrahydrofuran (2 mL) was  
10 treated with NaOH (80.0 mg, 2.0 mmols, 2.0 mL of a 1N aqueous solution)  
11 and stirred overnight at room temperature. Work-up afforded 24 mg (92%)  
12 the title compound as a pale-yellow solid.

13 <sup>1</sup>H NMR (d<sub>6</sub>-acetone) δ: 8.06 (2H, d, J = 8.2 Hz), 7.66 (2H, d, J = 8.2 Hz),  
14 7.58 (1H, s), 7.33 (2H, m), 3.87 (1H, m), 2.27 (2H, q, J = 7.0 Hz), 1.26 (6H, d,  
15 J = 6.7 Hz), 1.09 (2H, m), 0.99 (3H, t, J = 7.0 Hz), 0.88 (2H, m).

16 {4-[4-(1-Ethoxycyclopropyl)-3-isopropyl-phenylethynyl]-phenyl}-acetic acid

17 **(Compound 102, General Formula 2)**

18 Using General Procedure I; a solution of methyl {4-[4-(1-  
19 ethoxycyclopropyl)-3-isopropyl-phenylethynyl]-phenyl}-acetate (**Compound**  
20 **100**, 130.0 mg, 0.35 mmol) in ethanol (5 mL) and tetrahydrofuran (5 mL) was  
21 treated with NaOH (120.0 mg, 3.0 mmols, 3.0 mL of a 1N aqueous solution)  
22 and stirred at 50 °C for 4h. Work-up and isolation by HPLC (Partisil 10-pac,  
23 10% H<sub>2</sub>O/CH<sub>3</sub>CN) afforded 88.0 mg (70%) of the title compound.

24 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.50 (3H, m), 7.28-7.19 (4H, m), 3.82 (1H, m), 3.65 (2H,  
25 s), 3.29 (2H, q, J = 7.0 Hz), 1.25 (6H, d, J = 6.7 Hz), 1.14 (2H, m), 1.04 (3H, t,  
26 J = 7.0 Hz), 0.86 (2H, m).

27 4-Bromo-3-*tert*-butylphenol (**Intermediate 104**)

28 To a mixture of 3-*tert*-butyl-methoxy benzene (1.00 g, 6.09 mmols) in

1 CCl<sub>4</sub> (20 mL), molecular sieves, and silica gel was added *N*-bromosuccinimide  
2 (1.19 g, 6.70 mmols). This mixture was stirred at 55 °C for 48h. The resulting  
3 mixture was cooled to room temperature, filtered to remove the solids, and the  
4 filtrate diluted with EtOAc. This solution was washed with H<sub>2</sub>O, 10%  
5 aqueous HCl, H<sub>2</sub>O, saturated aqueous NaHCO<sub>3</sub> and saturated aqueous NaCl  
6 before being dried (MgSO<sub>4</sub>) and concentrated under reduced pressure.  
7 Column chromatography (2.5% EtOAc-hexanes) afforded 1.15 g (78%) of a 3  
8 to 1 mixture of 1-bromo-2-*tert*-butyl methoxy benzene and 1-bromo-2-  
9 methoxy-4-*tert*-butyl benzene as a colorless oil.

10 A solution of the isomeric methoxy compounds in 10 mL of CH<sub>2</sub>Cl<sub>2</sub>  
11 was cooled to 0 °C and treated with a solution (18.5 mL) of BBr<sub>3</sub> in CH<sub>2</sub>Cl<sub>2</sub>  
12 (4.63 g, 18.5 mmols). After 10 minutes the solution was warmed to room  
13 temperature, stirred for 1h, and then quenched with H<sub>2</sub>O. The mixture was  
14 extracted with EtOAc and the combined organic layers washed with saturated  
15 aqueous NaCl, dried (MgSO<sub>4</sub>), and concentrated under reduced pressure. The  
16 title compound was isolated, 1.17 g (59%), by column chromatography (2.5-  
17 5% EtOAc-hexanes).

18 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.39 (1H, d, J = 8.5 Hz), 6.96 (1H, d, J = 2.9 Hz), 6.54  
19 (1H, dd, J = 2.9, 8.5 Hz), 1.46 (9H, s).

20 (4-Bromo-3-*tert*-butyl-phenoxy)-triisopropyl-silane (Intermediate 105)

21 To a solution of 4-bromo-3-*tert*-butylphenol (Intermediate 104, 1.17 g,  
22 5.10 mmols) and imidazole (520.0 mg, 7.65 mmols) in 10 mL DMF was added  
23 chloro-triisopropylsilane (1.18 g, 6.10 mmols). After stirring overnight at  
24 room temperature the solution was diluted with H<sub>2</sub>O and extracted with  
25 EtOAc. The combined organic layers were washed with H<sub>2</sub>O and saturated  
26 aqueous NaCl before being dried (MgSO<sub>4</sub>) and concentrated under reduced  
27 pressure. The title compound, 1.80 g (92%), was isolated by column  
28 chromatography (0-1.5% EtOAc-hexanes) as a colorless oil.

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.38 (1H, d, J = 8.0 Hz), 6.97 (1H, d, J = 2.9 Hz), 6.56 (1H, dd, J = 2.9, 8.5 Hz), 1.47 (9H, s), 1.29-1.24 (3H, m), 1.09 (18H, d, J = 6.7 Hz).

Ethyl 2-*tert*-butyl-4-triisopropylsilanyloxy-benzoate (**Intermediate 106**)

To a solution of (4-bromo-3-*tert*-butyl-phenoxy)-triisopropyl-silane (**Intermediate 105**, 1.00 g, 2.60 mmols) in 15 mL Et<sub>2</sub>O cooled to -78 °C was added 3.6 mL of *tert*-butyllithium, 1.7 M in pentane (395.0 mg, 6.2 mmols). After stirring for 30 minutes ethyl chloroformate (607.6 mg, 5.6 mmols) was added. The resulting solution was warmed to room temperature and quenched by the addition of saturated aqueous NH<sub>4</sub>Cl. The mixture was extracted with EtOAc and the combined organic layers dried (MgSO<sub>4</sub>) concentrated under reduced pressure. The residue was chromatographed (2-5% EtOAc-hexanes) to give 1.23 g (88%) of the title compound as a colorless oil.

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.24 (1H, d, J = 8.2 Hz), 6.97 (1H, d, J = 2.6 Hz), 6.69 (1H, dd, J = 2.6, 8.2 Hz), 4.33 (2H, q, J = 7.1 Hz), 1.39 (9H, s), 1.37 (3H, t, J = 7.1 Hz), 1.29-1.21 (3H, m), 1.10 (18H, d, J = 6.7 Hz).

[4-(1-Ethoxyvinyl)-3-*tert*-butyl-phenoxy]-triisopropyl-silane (**Intermediate 107**)

Using General Procedure 1; ethyl 2-*tert*-butyl-4-triisopropylsilanyloxy-benzoate (**Intermediate 106**, 1.30 g, 3.44 mmols) and 7.2 mL of Tebbe's Reagent (1.03 g, 3.61 mmols) were reacted. The reaction required 7 days at room temperature to go to completion. The standard work-up afforded 1.29 g (78%) of the title compound after column chromatography (1-2% EtOAc-hexanes).

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.05 (1H, d, J = 8.2 Hz), 6.94 (1H, d, J = 2.6 Hz), 6.63 (1H, dd, J = 2.6, 8.2 Hz), 4.20 (1H, d, J = 1.7 Hz), 4.08 (1H, d, J = 1.7 Hz), 3.83 (2H, q, J = 7.1 Hz), 1.37 (9H, s), 1.36 (3H, t, J = 7.1 Hz), 1.27-1.20 (3H, m), 1.10 (18H, d, J = 6.7 Hz).

1 [4-(1-Ethoxycyclopropyl)-3-*tert*-butyl-phenoxy]-triisopropyl-silane

2 **(Intermediate 108)**

3       Using General Procedure 2; [4-(1-ethoxyvinyl)-3-*tert*-butyl-phenoxy]-  
4 triisopropyl-silane (**Intermediate 107**, 320.0 mg, 0.85 mmols), Et<sub>2</sub>Zn (325.0  
5 mg, 2.63 mmols), and CH<sub>2</sub>I<sub>2</sub> (704.0 mg, 2.63 mmols) in 5.0 mL Et<sub>2</sub>O afforded  
6 257.0 mg (66%) of the title compound as a colorless oil after chromatography  
7 (1-2.5% EtOAc - hexanes).

8 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.24 (1H, d, J = 8.5 Hz), 7.06 (1H, d, J = 2.6 Hz), 6.60  
9 (1H, dd, J = 2.6, 8.5 Hz), 3.24 (2H, q, J = 7.1 Hz), 1.50 (9H, s), 1.29-1.21 (3H,  
10 m), 1.11 (18H, d, J = 6.7 Hz), 1.04 (3H, t, J = 7.1 Hz).

11 4-(1-Ethoxycyclopropyl)-3-*tert*-butyl-phenol (**Intermediate 109**)

12       To a solution of [4-(1-ethoxycyclopropyl)-3-*tert*-butyl-phenoxy]-  
13 triisopropyl-silane (**Intermediate 108**, 600.0 mg, 1.54 mmol) in 3 mL THF at  
14 0 °C was added tetrabutylammonium fluoride (802.8.0 mg, 3.07 mmols; 3.1  
15 mL of a 1 M solution in THF). The solution was stirred at 0 °C for 30  
16 minutes and then quenched by the addition of H<sub>2</sub>O. The mixture was extracted  
17 with EtOAc and the combined organic layers were washed with H<sub>2</sub>O and  
18 saturated aqueous NaCl before being dried (MgSO<sub>4</sub>) and concentrated under  
19 reduced pressure. The title compound (400 mg, 88%) was isolated from the  
20 residue by column chromatography (4-10% EtOAc-hexanes) as a colorless  
21 solid.

22 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.29 (1H, d, J = 8.2 Hz), 7.01 (1H, d, J = 2.6 Hz), 6.57  
23 (1H, dd, J = 2.6, 8.2 Hz), 3.29 (2H, q, J = 7.1 Hz), 1.59 (9H, s), 1.08-1.04 (7H,  
24 m).

25 4-(1-Ethoxycyclopropyl)-3-*tert*-butyl-phenyl 1,1,1-trifluoromethanesulfonate  
26 **(Intermediate 110)**

27       A solution of 4-(1-ethoxycyclopropyl)-3-*tert*-butyl-phenol  
28 (**Intermediate 109**, 400.0 mg, 1.71 mmol) in 10 mL of CH<sub>2</sub>Cl<sub>2</sub> was cooled to

1 0 °C and to it was added 2-[N,N-bis(trifluoromethylsulfonyl)amino]-5-  
2 chloropyridine (705.0 mg, 1.79 mmol) and triethylamine (522.0 mg, 5.1  
3 mmols). The resulting solution was warmed to room temperature and stirred  
4 overnight. The reaction was quenched by the addition of H<sub>2</sub>O and the mixture  
5 extracted with EtOAc and the combined organic layers were washed with 10%  
6 aqueous HCl, saturated aqueous NaHCO<sub>3</sub>, H<sub>2</sub>O, and saturated aqueous NaCl.  
7 The solution was dried (MgSO<sub>4</sub>) and concentrated under reduced pressure.  
8 The title compound was isolated by column chromatography (2-4% EtOAc-  
9 hexanes) as a colorless oil, 542.0 mg (87%).  
10 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.48 (1H, d, J = 8.5 Hz), 7.39 (1H, d, J = 2.6 Hz), 7.01  
11 (1H, dd, J = 2.6, 8.5 Hz), 3.26 (2H, q, J = 7.1 Hz), 1.52 (9H, s), 1.12 (2H, bs),  
12 1.08-1.04 (5H, m).

13 [4-(1-Ethoxycyclopropyl)-3-*tert*-butyl-phenylethynyl]-trimethylsilane  
14 **(Intermediate 111)**

15 Using General Procedure D; 4-(1-ethoxycyclopropyl)-3-*tert*-butyl-  
16 phenyl 1,1,1-trifluoromethanesulfonate (**Intermediate 110**, 260.0 mg, 0.71  
17 mmol) in triethylamine (4 mL) and DMF (6 mL) was sparged with argon for 5  
18 minutes. Trimethylsilylacetylene (0.70 g, 7.1 mmols) was then added  
19 followed by dichlorobis-(triphenylphosphine)palladium(II) (40.0 mg, 0.06  
20 mmol). The resulting reaction mixture was heated to 95 °C for 18 hours. The  
21 title compound, 215.0 mg (96%), was isolated by chromatography (0 - 2%  
22 EtOAc - hexanes) as an orange oil.  
23 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.63 (1H, d, J = 1.7 Hz), 7.32 (1H, d, J = 7.9 Hz), 7.19  
24 (1H, dd, J = 1.7, 7.9 Hz), 3.24 (2H, q, J = 7.1 Hz), 1.51 (9H, s), 1.10 (2H, bs),  
25 1.06-1.01 (5H, m), 0.25 (9H, s).

26 1-(1-Ethoxycyclopropyl)-4-ethynyl-2-*tert*-butylbenzene (**Intermediate 112**)

27 Using General Procedure E; [4-(1-ethoxycyclopropyl)-3-*tert*-butyl-  
28 phenylethynyl]-trimethylsilane (**Intermediate 111**, 215.0 mg, 0.69 mmol) in

1 methanol (10 mL) was treated with potassium carbonate (80.0 mg, 0.58 mmol)  
2 and stirred overnight at ambient temperature. The crude alkyne, 169 mg, was  
3 used directly in the next reaction.

4 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.68 (1H, d, J = 1.8 Hz), 7.36 (1H, d, J = 7.9 Hz), 7.23  
5 (1H, dd, J = 1.8, 7.9 Hz), 3.26 (2H, q, J = 7.1 Hz), 3.06 (1H, s), 1.51 (9H, s),  
6 1.11 (2H, bs), 1.07-1.02 (5H, m).

7 Ethyl 4-[4-(1-ethoxycyclopropyl)-3-*tert*-butyl-phenylethynyl]-benzoate  
8 **(Compound 103, General Formula 2)**

9       Using General Procedure F; 1-(1-ethoxycyclopropyl)-4-ethynyl-2-*tert*-  
10 butylbenzene (**Intermediate 112**, 70.0 mg, 0.30 mmol) and ethyl-4-iodo  
11 benzoate (**Reagent A**, 85.0 mg, 0.30 mmol) in triethylamine (5 mL) was  
12 treated with copper(I)iodide (19.0 mg, 0.01 mmol) and sparged with argon for  
13 5 minutes. Dichlorobis(triphenylphosphine)-palladium(II) (70 mg, 0.01  
14 mmol) was added and the reaction mixture was stirred overnight at room  
15 temperature. Column chromatography (1-2% EtOAc - hexanes) afforded 70.0  
16 mg (73%) of the title compound.

17 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 8.02 (2H, d, J = 8.8 Hz), 7.72 (1H, d, J = 1.7 Hz), 7.59  
18 (2H, d, J = 8.8 Hz), 7.40 (1H, d, J = 7.9 Hz), 7.28 (1H, dd, J = 1.7, 7.9 Hz),  
19 4.39 (2H, q, J = 7.1 Hz), 3.28 (2H, q, J = 7.1 Hz), 1.55 (9H, s), 1.40 (3H, t, J =  
20 7.1 Hz), 1.12 (2H, bs), 1.08-1.04 (5H, m).

21 Methyl {4-[4-(1-ethoxycyclopropyl)-3-*tert*-butyl-phenylethynyl]-phenyl}-  
22 acetate **(Compound 104, General Formula 2)**

23       Using General Procedure F; 1-(1-ethoxycyclopropyl)-4-ethynyl-2-*tert*-  
24 butylbenzene (**Intermediate 112**, 95.0 mg, 0.39 mmol) and methyl-(4-  
25 iodophenyl)-acetate (**Reagent B**, 108.0 mg, 0.39 mmol) in triethylamine (8  
26 mL) was treated with copper(I)iodide (25.0 mg, 0.13 mmol) and sparged with  
27 argon for 5 minutes. Dichlorobis(triphenylphosphine)palladium(II) (91 mg,  
28 0.13 mmol) was added and the reaction mixture was stirred overnight at room

1 temperature. Column chromatography (2-5% EtOAc - hexanes) afforded  
2 100.0 mg (72%) of the title compound.

3 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.70 (1H, d, J = 1.5 Hz), 7.50 (2H, d, J = 7.9 Hz), 7.38  
4 (1H, d, J = 7.9 Hz), 7.27 (3H, m), 3.70 (3H, s), 3.64 (2H, s), 3.28 (2H, q, J =  
5 7.1 Hz), 1.54 (9H, s), 1.12 (2H, bs), 1.08-1.03 (5H, m).

6 4-[4-(1-Ethoxycyclopropyl)-3-*tert*-butyl-phenylethynyl]-benzoic acid

7 **(Compound 105, General Formula 2)**

8 Using General Procedure I; a solution of ethyl 4-[4-(1-  
9 ethoxycyclopropyl)-3-*tert*-butyl-phenylethynyl]-benzoate (**Compound 103**,  
10 70.0 mg, 0.18 mmol) in ethanol (3 mL) and tetrahydrofuran (3 mL) was  
11 treated with NaOH (240.0 mg, 6.0 mmols, 3.0 mL of a 2N aqueous solution)  
12 and stirred overnight at room temperature. Work-up afforded 40 mg (62%)  
13 the title compound as a pale-yellow solid.

14 <sup>1</sup>H NMR (d<sub>6</sub>-acetone) δ: 8.06 (2H, d, J = 8.7 Hz), 7.76 (1H, d, J = 1.8 Hz),  
15 7.67 (2H, d, J = 8.7 Hz), 7.50 (1H, d, J = 7.9 Hz), 7.33 (1H, dd, J = 1.8, 7.9  
16 Hz), 3.28 (2H, q, J = 7.3 Hz), 1.54 (9H, s), 1.13 (2H, bs), 1.10 (2H, m), 1.02  
17 (3H, t, J = 7.3 Hz).

18 {4-[4-(1-Ethoxycyclopropyl)-3-*tert*-butyl-phenylethynyl]-phenyl}-acetic acid

19 **(Compound 106, General Formula 2)**

20 Using General Procedure I; a solution of methyl {4-[4-(1-  
21 ethoxycyclopropyl)-3-*tert*-butyl-phenylethynyl]-phenyl}-acetate (**Compound**  
22 **104**, 100.0 mg, 0.26 mmol) in ethanol (4 mL) and tetrahydrofuran (4 mL) was  
23 treated with NaOH (240.0 mg, 6.0 mmols, 3.0 mL of a 2N aqueous solution)  
24 and stirred at 50 °C for 4h. Work-up and isolation by HPLC (Partisil 10-pac,  
25 10% H<sub>2</sub>O/CH<sub>3</sub>CN) afforded 70.0 mg (73%) of the title compound.

26 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.73 (1H, d, J = 1.3 Hz), 7.53 (2H, d, J = 7.9 Hz), 7.41  
27 (1H, d, J = 7.9 Hz), 7.28 (3H, m), 3.69 (2H, s), 3.31 (2H, q, J = 7.1 Hz), 1.56  
28 (9H, s), 1.15 (2H, bs), 1.11-1.05 (5H, m).

1 1-(4-Bromophenyl)-cyclopropanecarbonitrile (Intermediate 113)

2 To a 50% aqueous NaOH solution (40.0 g, wt/wt) was added benzyl  
3 triethylammonium chloride (1.0 g, 4.4 mmols), 4-bromobenzonitrile (19.6 g,  
4 0.10 mol), and 1,2-dibromoethane (56.4 g, 0.30 mol). The mixture was stirred  
5 overnight at room temperature and then diluted with 100 mL of H<sub>2</sub>O. This  
6 mixture was extracted with EtOAc and the combined extracts were washed  
7 with saturated aqueous NaHS<sub>2</sub>O<sub>3</sub>, H<sub>2</sub>O, and saturated aqueous NaCl before  
8 being dried (MgSO<sub>4</sub>) and concentrated under reduced pressure. Bulb-to-bulb  
9 distillation afforded 18.8 g (85%) of the title compound as a colorless solid.  
10 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.48 (2H, d, J = 8.6 Hz), 7.17 (2H, d, J = 8.6 Hz), 1.75  
11 (2H, dd, J = 5.2, 7.6 Hz), 1.39 (2H, dd, J = 5.2, 7.6 Hz).

12 1-(4-Bromophenyl)-cyclopropanecarboxylic acid (Intermediate 114)

13 To a solution of KOH (6.06 g, 0.11 mol) in 10 mL of H<sub>2</sub>O was added  
14 40 mL of ethylene glycol and 1-(4-bromophenyl)-cyclopropanecarbonitrile  
15 (Intermediate 113, 10.0 g, 0.45 mol). This solution was heated to 135-140 °C  
16 for 4h, cooled to room temperature, and then poured into a mixture of 100 mL  
17 ice and 10% aqueous HCl. The resulting mixture was allowed to stand  
18 overnight at 5 °C, the solid was collected by filtration and washed with H<sub>2</sub>O.  
19 The colorless solid was dried under reduced pressure to give 10.6 g (97%) of  
20 the title compound.

21 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.43 (2H, d, J = 8.5 Hz), 7.21 (2H, d, J = 8.5 Hz), 1.68  
22 (2H, dd, J = 4.0, 7.1 Hz), 1.24 (2H, dd, J = 4.0, 7.1 Hz).

23 Tert-butyl [1-(4-bromophenyl)-cyclopropyl]-carbamate (Intermediate 115)

24 A solution of 1-(4-bromophenyl)-cyclopropanecarboxylic acid  
25 (Intermediate 114, 2.32 g, 9.62 mmols), diphenylphosphoryl azide (2.65 g,  
26 9.62 mmols), triethylamine (973.0 mg, 9.62 mmols) in 40 mL *tert*-BuOH  
27 (distilled from Na<sup>o</sup>) was heated to reflux for 17h. The solution was  
28 concentrated under reduced pressure and the residue dissolved in EtOAc and



1 washed with 5% aqueous HCl, H<sub>2</sub>O, saturated aqueous NaHCO<sub>3</sub>, and saturated  
2 aqueous NaCl before being dried over MgSO<sub>4</sub>. Concentration of the dry  
3 solution under reduced pressure and column chromatography (5-10% EtOAc -  
4 hexanes) afforded 2.01 g (67%) of the title compound as a colorless solid.  
5 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.39 (2H, d, J = 8.3 Hz), 7.08 (2H, d, J = 8.3 Hz), 5.35  
6 (1H, bs), 1.43 (9H, s), 1.26 (2H, m), 1.17 (2H, m).

7 1-(4-Bromophenyl)-cyclopropylamine (Intermediate 116)

8 To a solution of *tert*-butyl [1-(4-bromophenyl)-cyclopropyl]-carbamate  
9 (**Intermediate 115**, 1.08 g, 3.40 mmols) in 20 mL MeOH and 20 mL THF was  
10 added 20 mL of 3M aqueous HCl. The solution was warmed to 35 °C for 3  
11 hours and then stirred for 17h at 25 °C. The reaction was quenched by  
12 adjusting the pH of the solution to 12 with 3M aqueous NaOH. The mixture  
13 was extracted with Et<sub>2</sub>O and the combined organic layers were washed with  
14 H<sub>2</sub>O and saturated aqueous NaCl before being dried (MgSO<sub>4</sub>) and  
15 concentrated under reduced pressure. The title compound 613 mg (85%) was  
16 used without further purification.

17 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.43 (2H, d, J = 8.3 Hz), 7.17 (2H, d, J = 8.3 Hz), 1.89  
18 (2H, bs), 1.07 (2H, m), 0.95 (2H, m).

19 N-[1-(4-bromophenyl)-cyclopropyl]-propionamide (Intermediate 117)

20 To a solution of 1-(4-bromophenyl)-cyclopropylamine (**Intermediate**  
21 **116**, 84 mg, 0.4 mmol) in 4 mL CH<sub>2</sub>Cl<sub>2</sub> at room temperature was added  
22 propionyl chloride (43.0 mg, 0.47 mmol) and pyridine (56.0 mg, 0.71 mmol).  
23 After stirring 17 hours at room temperature the reaction was quenched by the  
24 addition of H<sub>2</sub>O and extracted with EtOAc. The combined extracts were  
25 washed with 10% aqueous HCl, saturated aqueous NaHCO<sub>3</sub>, and saturated  
26 aqueous NaCl before being dried (MgSO<sub>4</sub>) and concentrated under reduced  
27 pressure. The title compound 85.0 mg (67%), was isolated by column  
28 chromatography (20-50% EtOAc-hexanes) as a colorless solid.

1 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.48 (2H, d, J = 8.5 Hz), 7.09 (2H, d, J = 8.5 Hz), 6.40  
2 (1H, s), 2.19 (2H, q, J = 7.2 Hz), 1.18-1.24 (4H, m), 1.12 (3H, t, J = 7.2 Hz).

3 [1-(4-Bromophenyl)-cyclopropyl]-propylamine (Intermediate 118)

4 To a solution of *N*-[1-(4-bromophenyl)-cyclopropyl]-propionamide  
5 (**Intermediate 117**, 85.0 mg, 0.32 mmol) in THF (5 mL) at 0 °C was added  
6 BH<sub>3</sub>-Me<sub>2</sub>S (48.0 mg, 0.63 mmol; 0.31 mL of a 2M solution in THF). The  
7 solution was heated to 55 °C for 17 hours, cooled to room temperature,  
8 saturated aqueous NaHCO<sub>3</sub> was added and the resulting mixture was stirred  
9 for 2 hours. This mixture was extracted with EtOAc and the combined organic  
10 layers were washed with H<sub>2</sub>O and saturated aqueous NaCl before being dried  
11 (MgSO<sub>4</sub>) and concentrated under reduced pressure. The title compound was  
12 isolated by column chromatography (10-30% EtOAc-hexanes).

13 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.42 (2H, d, J = 8.5 Hz), 7.19 (2H, d, J = 8.5 Hz), 2.46  
14 (2H, t, J = 7.3 Hz), 1.40 (2H, m), 0.98 (2H, m), 0.86 (5H, m).

15 Propyl-[1-(4-trimethylsilanylethynyl-phenyl)-cyclopropyl]-amine  
16 (**Intermediate 119**)

17 Using General Procedure D; [1-(4-bromophenyl)-cyclopropyl]-  
18 propylamine (**Intermediate 118**, 100.0 mg, 0.39 mmol) in triethylamine (8  
19 mL) was treated with copper(I)iodide (13.0 mg, 0.06 mmol) and then sparged  
20 with argon for 5 minutes. Trimethylsilyl acetylene (0.70 g, 7.1 mmols) was  
21 then added followed by dichlorobis(triphenylphosphine)palladium(II) (48.0  
22 mg, 0.06 mmol). The resulting reaction mixture was heated to 70 °C for  
23 5 days. The title compound (80.0 mg, 75%) was isolated by chromatography  
24 (0 - 10% EtOAc - hexanes) as an orange oil.

25 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.41 (2H, d, J = 8.5 Hz), 7.21 (2H, d, J = 8.5 Hz), 2.45  
26 (2H, t, J = 7.3 Hz), 1.39 (2H, m), 0.98 (2H, m), 0.87 (2H, m), 0.84 (3H, t, J =  
27 7.3 Hz), 0.24 (9H, s).

28 [1-(4-Ethynylphenyl)-cyclopropyl]-propylamine (Intermediate 120)

1       Using General Procedure E; propyl-[1-(4-trimethylsilanylethynyl-  
2 phenyl)-cyclopropyl]-amine (**Intermediate 119**, 80.0 mg, 0.30 mmols) in  
3 methanol (8 mL) was treated with potassium carbonate (80.0 mg, 0.59 mmol)  
4 and stirred overnight at ambient temperature. The crude alkyne (58 mg,  
5 100%) was used directly in the next reaction.

6 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.44 (2H, d, J = 8.5 Hz), 7.24 (2H, d, J = 8.5 Hz), 3.05  
7 (1H, s), 2.46 (2H, t, J = 7.3 Hz), 1.41 (2H, m), 1.00 (2H, m), 0.90 (2H, m),  
8 0.86 (3H, t, J = 7.3 Hz).

9 Ethyl 4-[4-(1-propylamino-cyclopropyl)-phenylethynyl]-benzoate  
10 (**Compound 107**, General Formula 2)

11       Using General Procedure F; [1-(4-ethynylphenyl)-cyclopropyl]-  
12 propylamine (**Intermediate 120**, 38.0 mg, 0.19 mmol) and ethyl-4-iodo  
13 benzoate (**Reagent A**, 58.0 mg, 0.21 mmol) in triethyl amine (6 mL) was  
14 treated with copper(I)iodide (8.0 mg, 0.04 mmol) and sparged with argon for 5  
15 minutes. Dichlorobis(triphenylphosphine)palladium(II) (27 mg, 0.04 mmol)  
16 was added and the reaction mixture was stirred overnight at room temperature.  
17 Column chromatography (5-15% EtOAc - hexanes) afforded 40.0 mg (61%)  
18 of the title compound as an orange oil.

19 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 8.01 (2H, d, J = 8.5 Hz), 7.57 (2H, d, J = 8.5 Hz), 7.49  
20 (2H, d, J = 8.5 Hz), 7.28 (2H, d, J = 8.5 Hz), 4.39 (2H, q, J = 7.1 Hz), 2.49  
21 (2H, t, J = 7.3 Hz), 1.46 (2H, m), 1.41 (3H, t, J = 7.1 Hz), 1.01 (2H, m), 0.89  
22 (2H, m), 0.87 (3H, t, J = 7.3 Hz).

23 4-[4-(1-Propylamino-cyclopropyl)-phenylethynyl]-benzoic acid (**Compound**  
24 **108**, General Formula 2)

25       Using General Procedure I; a solution of ethyl 4-[4-(1-propylamino-  
26 cyclopropyl)-phenylethynyl]-benzoate (**Compound 107**, 40.0 mg, 0.12 mmol)  
27 in ethanol (3 mL) and tetrahydrofuran (3 mL) was treated with NaOH (160.0  
28 mg, 4.0 mmols, 2.0 mL of a 2N aqueous solution) and stirred overnight at

1 room temperature. Work-up afforded 25.0 mg (69%) of the title compound as  
2 a solid.

3 <sup>1</sup>H NMR (d<sub>6</sub>-DMSO) δ: 7.97 (2H, d, J = 8.5 Hz), 7.65 (2H, d, J = 8.5 Hz), 7.50  
4 (2H, d, J = 8.5 Hz), 7.36 (2H, d, J = 8.5 Hz), 2.39 (2H, t, J = 7.3 Hz), 1.37 (2H,  
5 m), 1.00 (2H, m), 0.93 (2H, m), 0.84 (3H, t, J = 7.3 Hz).

6 [1-(4-Bromophenyl)-cyclopropyl]-dipropylamine (Intermediate 121)

7 To a solution of 1-(4-bromophenyl)-cyclopropylamine (**Intermediate**  
8 **116**) in CH<sub>3</sub>CN / HOAc (5 mL, 9:1, v/v) and THF 3 mL at 0 °C was added  
9 propionaldehyde (277.0 mg, 4.95 mmols) and NaCNBH<sub>3</sub> (153.0 mg, 2.47  
10 mmols). The reaction was warmed to room temperature and after 5 hours  
11 quenched with H<sub>2</sub>O. The pH of the solution was adjusted to 8-9 using aqueous  
12 NaOH and extracted with EtOAc. The combined extracts were washed with  
13 H<sub>2</sub>O and saturated aqueous NaCl, dried (MgSO<sub>4</sub>) and concentrated under  
14 reduced pressure. The title compound, 190.0 mg (56%), was isolated by  
15 column chromatography (2-5% EtOAc-hexanes).

16 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.42 (2H, d, J = 8.3 Hz), 7.18 (2H, d, J = 8.3 Hz), 2.39  
17 (4H, t, J = 7.3 Hz), 1.62-1.40 (4H, m), 0.96 (2H, m), 0.86 (6H, t, J = 7.3 Hz),  
18 0.80 (2H, m).

19 Dipropyl-[1-(4-trimethylsilanylethynyl-phenyl)-cyclopropyl]-amine  
20 (**Intermediate 122**)

21 Using General Procedure D; [1-(4-bromophenyl)-cyclopropyl]-  
22 dipropylamine (**Intermediate 121**, 150.0 mg, 0.50 mmol) in triethylamine (5  
23 mL) was treated with copper(I)iodide (10.0 mg, 0.05 mmol) and then sparged  
24 with argon for 5 minutes. Trimethylsilyl acetylene (0.70 g, 7.1 mmols) was  
25 then added followed by dichlorobis(triphenylphosphine)palladium(II) (35.0  
26 mg, 0.05 mmol). The resulting reaction mixture was heated to 70 °C for 5d.  
27 The title compound was isolated by chromatography (0 - 3% EtOAc -  
28 hexanes).

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.35 (2H, d, J = 8.3 Hz), 7.24 (2H, d, J = 8.3 Hz), 2.39 (4H, t, J = 7.3 Hz), 1.55-1.42 (4H, m), 0.96 (2H, m), 0.88-0.79 (8H, m), 0.25 (9H, s).

[1-(4-Ethynylphenyl)-cyclopropyl]-dipropylamine (Intermediate 123)

Using General Procedure E; dipropyl-[1-(4-trimethylsilanylethynyl-phenyl)-cyclopropyl]-amine (**Intermediate 122**, 45.0 mg, 0.14 mmols) in methanol (5 mL) was treated with potassium carbonate (50.0 mg, 0.37 mmol) and stirred overnight at ambient temperature. The crude alkyne (34 mg, 100%) was used directly in the next reaction.

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.42 (2H, d, J = 8.3 Hz), 7.28 (2H, d, J = 8.3 Hz), 2.40 (4H, t, J = 7.3 Hz), 1.53-1.40 (4H, m), 0.96 (2H, m), 0.90-0.79 (8H, m).

Ethyl 4-[4-(1-dipropylamino-cyclopropyl)-phenylethynyl]-benzoate  
(**Compound 109, General Formula 2**)

Using General Procedure F; [1-(4-ethynylphenyl)-cyclopropyl]-dipropylamine (**Intermediate 123**, 34.0 mg, 0.16 mmol) and ethyl-4-iodobenzoate (**Reagent A**, 59.0 mg, 0.21 mmol) in triethyl amine (6 mL) was treated with copper(I)iodide (13.0 mg, 0.07 mmol) and sparged with argon for 5 minutes. Dichlorobis(triphenylphosphine)palladium(II) (49 mg, 0.07 mmol) was added and the reaction mixture was stirred overnight at room temperature. Column chromatography (2-4% EtOAc - hexanes) afforded the title compound as a yellow oil.

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 8.03 (2H, d, J = 8.2 Hz), 7.58 (2H, d, J = 8.2 Hz), 7.49 (2H, d, J = 8.2 Hz), 7.30 (2H, d, J = 8.2 Hz), 4.39 (2H, q, J = 7.1 Hz), 2.43 (4H, t, J = 7.3 Hz), 1.52-1.42 (4H, m), 1.41 (3H, t, J = 7.1 Hz), 0.99 (2H, m), 0.88-0.83 (8H, m).

4-[4-(1-Dipropylamino-cyclopropyl)-phenylethynyl]-benzoic acid  
(**Compound 110, General Formula 2**)

Using General Procedure I; a solution of ethyl 4-[4-(1-dipropylamino-

1 cyclopropyl)-phenylethynyl]-benzoate (**Compound 109**, 51.0 mg, 0.13 mmol)  
2 in ethanol (3 mL) and tetrahydrofuran (3 mL) was treated with NaOH (80.0  
3 mg, 2.0 mmols, 2.0 mL of a 1N aqueous solution) and stirred overnight at  
4 room temperature. Work-up afforded 32.0 mg (70%) of the title compound as  
5 a colorless solid.

6 <sup>1</sup>H NMR (d<sub>6</sub>-DMSO) δ: 7.98 (2H, d, J = 8.3 Hz), 7.67 (6H, m), 3.05-2.89 (4H,  
7 m), 1.98 (2H, m), 1.72 (4H, m), 1.23 (2H, m), 0.88 (6H, t, J = 7.3 Hz).

8 Benzyl-[1-(4-bromophenyl)-cyclopropyl]-amine (**Intermediate 124**) and  
9 Dibenzyl-[1-(4-bromophenyl)-cyclopropyl]-amine (**Intermediate 125**)

10 A solution of 1-(4-bromophenyl)-cyclopropylamine (**Intermediate 116**,  
11 244.0 mg, 1.15 mmols) and benzyl bromide (255.0 mg, 1.50 mmols) in 4 mL  
12 DMF was stirred at 85 °C for 6 hours, cooled to room temperature and stirred  
13 overnight. The solution was diluted with H<sub>2</sub>O and the pH adjusted to 8-9 with  
14 aqueous NaOH. The solution was extracted with EtOAc and the combined  
15 organic layers were washed with H<sub>2</sub>O and saturated aqueous NaCl, dried  
16 (MgSO<sub>4</sub>) and concentrated under reduced pressure. Column chromatography  
17 (5-10% EtOAc-Hexanes) afforded 110 mg (32%) of the *N*-benzyl amine.  
18 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.48 (2H, d, J = 8.4 Hz), 7.30-7.23 (7H, m), 3.68 (2H, s),  
19 1.07 (2H, m), 0.93 (2H, m); and 100 mg (22%) of the *N,N*-dibenzyl amine, <sup>1</sup>H  
20 NMR (CDCl<sub>3</sub>) δ: 7.55 (2H, d, J = 8.3 Hz), 7.40-7.19 (12H, m), 3.61 (4H, s),  
21 0.87 (2H, m), 0.71 (2H, m).

22 Benzyl-[1-(4-trimethylsilanylethynyl-phenyl)-cyclopropyl]-amine  
23 (**Intermediate 126**)

24 Using General Procedure D; benzyl-[1-(4-bromophenyl)-cyclopropyl]-  
25 amine (**Intermediate 124**, 110.0 mg, 0.36 mmol) in triethylamine (8 mL) was  
26 treated with copper(I)iodide (10.0 mg, 0.05 mmol) and then sparged with  
27 argon for 5 minutes. Trimethylsilyl acetylene (0.70 g, 7.1 mmols) was then  
28 added followed by dichlorobis(triphenylphosphine)palladium(II) (38.0 mg,

0.05 mmol). The resulting reaction mixture was heated to 70 °C for 5d. The title compound 85 mg (74%) was isolated by chromatography (1 - 10% EtOAc - hexanes).

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.46 (2H, d, J = 8.3 Hz), 7.31-7.22 (7H, m), 3.67 (2H, s), 1.06 (2H, m), 0.94 (2H, m), 0.26 (9H, s).

**Benzyl-[1-(4-ethynylphenyl)-cyclopropyl]-amine (Intermediate 127)**

Using General Procedure E; benzyl-[1-(4-trimethylsilanylethynyl-phenyl)-cyclopropyl]-amine (**Intermediate 126**, 85.0 mg, 0.27 mmol) in methanol (5 mL) was treated with potassium carbonate (50.0 mg, 0.37 mmol) and stirred overnight at ambient temperature. The crude alkyne (65 mg, 100%) was used directly in the next reaction.

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.49 (2H, d, J = 7.9 Hz), 7.32 (2H, d, J = 7.9 Hz), 7.23 (5H, m), 3.68 (2H, s), 3.08 (1H, s), 1.07 (2H, m), 0.95 (2H, m).

**Ethyl 4-[4-(1-benzylamino-cyclopropyl)-phenylethynyl]-benzoate (Compound 111, General Formula 2)**

Using General Procedure F; benzyl-[1-(4-ethynylphenyl)-cyclopropyl]-amine (**Intermediate 127**, 65.0 mg, 0.27 mmol) and ethyl-4-iodo benzoate (**Reagent A**, 68.0 mg, 0.27 mmol) in triethyl amine (8 mL) was treated with copper(I)iodide (16.0 mg, 0.08 mmol) and sparged with argon for 5 minutes. Dichlorobis (triphenylphosphine)palladium(II) (58 mg, 0.08 mmol) was added and the reaction mixture was stirred overnight at room temperature. Column chromatography (2-5% EtOAc - hexanes) afforded 90 mg (90%) of the title compound as an orange solid.

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 8.05 (2H, d, J = 8.3 Hz), 7.61 (2H, d, J = 8.3 Hz), 7.55 (2H, d, J = 8.1 Hz), 7.43 (2H, d, J = 8.1 Hz), 7.32-7.22 (5H, m), 4.40 (2H, q, J = 7.1 Hz), 3.72 (2H, s), 1.42 (2H, t, J = 7.1 Hz), 1.01 (2H, m), 0.99 (2H, m).

**4-[4-(1-Benzylamino-cyclopropyl)-phenylethynyl]-benzoic acid (Compound 112, General Formula 2)**

1       Using General Procedure I; a solution of ethyl 4-[4-(1-benzylamino-  
2 cyclopropyl)-phenylethynyl]-benzoate (**Compound 111**, 75.0 mg, 0.19 mmol)  
3 in ethanol (4 mL) and tetrahydrofuran (4 mL) was treated with NaOH (80.0  
4 mg, 2.0 mmols, 2.0 mL of a 1N aqueous solution) and stirred overnight at  
5 room temperature. Work-up afforded 35.0 mg (50%) of the title compound as  
6 a colorless solid.

7 <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ: 7.93 (2H, d, J = 8.3 Hz), 7.61-7.51 (6H, m), 7.32-7.23  
8 (5H, m), 3.98 (2H, s), 1.33(2H, m), 1.19 (2H, m).

9 Dibenzyl-[1-(4-trimethylsilanylethynyl-phenyl)-cyclopropyl]-amine  
10 (**Intermediate 128**)

11       Using General Procedure D; dibenzyl-[1-(4-bromophenyl)-  
12 cyclopropyl]-amine (**Intermediate 125**, 45.0 mg, 0.11 mmol) in triethylamine  
13 (8 mL) was treated with copper(I)iodide (10.0 mg, 0.05 mmol) and then  
14 sparged with argon for 5 minutes. Trimethylsilyl acetylene (0.35 g, 3.6  
15 mmols) was then added followed by  
16 dichlorobis(triphenylphosphine)palladium(II) (35.0 mg, 0.05 mmol). The  
17 resulting reaction mixture was heated to 70 °C for 5d. The title compound 40  
18 mg (88%) was isolated by chromatography (hexanes).

19 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.52 (2H, d, J = 8.3 Hz), 7.36-7.24 (12H, m), 3.60 (4H, s),  
20 0.87 (2H, m), 0.67 (2H, m), 0.29 (9H, s).

21 Dibenzyl-[1-(4-ethynylphenyl)-cyclopropyl]-amine (**Intermediate 129**)

22       Using General Procedure E; dibenzyl-[1-(4-trimethylsilanylethynyl-  
23 phenyl)-cyclopropyl]-amine (**Intermediate 128**, 100.0 mg, 0.26 mmol) in  
24 methanol (5 mL) was treated with potassium carbonate (60.0 mg, 0.44 mmol)  
25 and stirred overnight at ambient temperature. The crude alkyne (80 mg, 99%)  
26 was used directly in the next reaction.

27 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.53 (2H, d, J = 7.9 Hz), 7.36 (2H, d, J = 7.9 Hz), 7.28-  
28 7.25 (10H, m), 3.62 (4H, s), 3.11 (1H, s), 0.88 (2H, m), 0.68 (2H, m).



1 Ethyl 4-[4-(1-dibenzylamino-cyclopropyl)-phenylethynyl]-benzoate

2 **(Compound 113, General Formula 2)**

3       Using General Procedure F; dibenzyl-[1-(4-ethynylphenyl)-  
4 cyclopropyl]-amine (**Intermediate 129**, 40.0 mg, 0.12 mmol) and ethyl-4-iodo  
5 benzoate (**Reagent A**, 60.0 mg, 0.22 mmol) in triethylamine (5 mL) was  
6 treated with copper(I)iodide (8.0 mg, 0.04 mmol) and sparged with argon for 5  
7 minutes. Dichlorobis (triphenylphosphine)palladium(II) (27 mg, 0.04 mmol)  
8 was added and the reaction mixture was stirred overnight at room temperature.  
9 Column chromatography (2-5% EtOAc - hexanes) afforded the title compound  
10 as an oil.

11 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 8.04 (2H, d, J = 8.5 Hz), 7.79 (4H, m), 7.42 (2H, d, J =  
12 7.9 Hz), 7.29-7.17 (10H, m), 4.40 (2H, q, J = 7.1 Hz), 3.63 (4H, s), 1.42 (3H, t,  
13 J = 7.1 Hz), 0.88 (2H, m), 0.73 (2H, m).

14 4-[4-(1-Dibenzylamino-cyclopropyl)-phenylethynyl]-benzoic acid

15 **(Compound 114, Formula 2)**

16       Using General Procedure I; a solution of ethyl 4-[4-(1-dibenzylamino-  
17 cyclopropyl)-phenylethynyl]-benzoate (**Compound 113**, 48.0 mg, 0.10 mmol)  
18 in ethanol (2 mL) and tetrahydrofuran (2 mL) was treated with NaOH (80.0  
19 mg, 2.0 mmols, 2.0 mL of a 1N aqueous solution) and stirred overnight at  
20 room temperature. Work-up afforded 42.0 mg (93%) of the title compound as  
21 a colorless solid.

22 <sup>1</sup>H NMR (d<sub>6</sub>-DMSO) δ: 7.98 (2H, d, J = 8.2 Hz), 7.67 (2H, d, J = 8.2 Hz), 7.64  
23 (2H, d, J = 7.9 Hz), 7.47 (2H, d, J = 7.9 Hz), 7.28-7.20 (10H, m), 3.57 (4H, s),  
24 0.84 (2H, m), 0.69 (2H, m).

25 Benzyl-[1-(4-bromophenyl)-cyclopropyl]-methylamine (**Intermediate 130**)

26       To a solution of benzyl-[1-(4-bromophenyl)-cyclopropyl]-amine  
27 (**Intermediate 124**, 100.0 mg, 0.33 mmol) in 5 mL of acetone was added  
28 K<sub>2</sub>CO<sub>3</sub> (91 mg, 0.66 mmol) and iodomethane (2.28 g, 16.1 mmols). The

1 resulting mixture was stirred at 25 °C for 20 hours, diluted with Et<sub>2</sub>O, and  
2 washed with H<sub>2</sub>O and saturated aqueous NaCl. The solution was dried  
3 (MgSO<sub>4</sub>) and concentrated under reduced pressure to give 90 mg (86%) of the  
4 title compound.

5 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.47 (2H, d, J = 8.5 Hz), 7.29-7.18 (7H, m), 3.53 (2H, s),  
6 2.07 (3H, s), 1.07 (2H, m), 0.86 (2H, m).

7 Benzyl-[1-(4-trimethylsilanylethynyl)-phenyl]-cyclopropyl]-methylamine  
8 **(Intermediate 131)**

9 Using General Procedure D; benzyl-[1-(4-bromophenyl)-cyclopropyl]-  
10 methylamine (**Intermediate 130**, 90.0 mg, 0.28 mmol) in triethylamine (8  
11 mL) was treated with copper(I)iodide (6.0 mg, 0.03 mmol) and then sparged  
12 with argon for 5 minutes. Trimethylsilyl acetylene (0.70 g, 7.1 mmols) was  
13 then added followed by dichlorobis(triphenylphosphine)palladium(II) (20.0  
14 mg, 0.03 mmol). The resulting reaction mixture was heated to 70 °C for 5  
15 days. The title compound 80 mg (84%) was isolated by chromatography (0-  
16 2% EtOAc-hexanes).

17 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.46 (2H, d, J = 8.2 Hz), 7.32-7.18 (7H, m), 3.52 (2H, s),  
18 2.06 (3H, s), 1.06 (2H, m), 0.87(2H, m), 0.26 (9H, s).

19 Benzyl-[1-(4-ethynylphenyl)-cyclopropyl]-methylamine (**Intermediate 132**)

20 Using General Procedure E; benzyl-[1-(4-trimethylsilanylethynyl-  
21 phenyl)-cyclopropyl]-methylamine (**Intermediate 131**, 80.0 mg, 0.24 mmol)  
22 in methanol (5 mL) was treated with potassium carbonate (80.0 mg, 0.59  
23 mmol) and stirred overnight at ambient temperature. The crude alkyne (60  
24 mg, 99%) was used directly in the next reaction.

25 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.49 (2H, d, J = 8.2 Hz), 7.33-7.21 (7H, m), 3.55 (2H, s),  
26 3.08 (1H, s), 2.08 (3H, s), 1.07 (2H, m), 0.89 (2H, m).

27 Ethyl 4-{4-[1-(benzyl-methylamino)-cyclopropyl]-phenylethynyl}-benzoate  
28 **(Compound 115, General Formula 2)**

1       Using General Procedure F; benzyl-[1-(4-ethynylphenyl)-cyclopropyl]-  
2 methylamine (**Intermediate 132**, 70.0 mg, 0.28 mmol) and ethyl-4-iodo  
3 benzoate (**Reagent A**, 77.0 mg, 0.28 mmol) in triethylamine (5 mL) was  
4 treated with copper(I)iodide (18.0 mg, 0.10 mmol) and sparged with argon for  
5 5 minutes. Dichlorobis (triphenylphosphine)palladium(II) (65 mg, 0.10 mmol)  
6 was added and the reaction mixture was stirred overnight at room temperature.  
7 Column chromatography (2-5% EtOAc - hexanes) afforded 86 mg (75%) of  
8 the title compound as an oil.

9 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 8.03 (2H, d, J = 8.5 Hz), 7.59 (2H, d, J = 8.5 Hz), 7.53  
10 (2H, d, J = 8.2 Hz), 7.36 (2H, d, J = 8.2 Hz), 7.25 (5H, m), 4.39 (2H, q, J = 7.1  
11 Hz), 3.57 (2H, s), 2.10 (3H, s), 1.41 (3H, t, J = 7.1 Hz), 1.10 (2H, m), 0.92  
12 (2H, m).

13 4-[4-(1-Benzylmethylamino-cyclopropyl)-phenylethynyl]-benzoic acid  
14 (**Compound 116, General Formula 2**)

15       Using General Procedure I; a solution of ethyl 4-{4-[1-(benzyl-  
16 methylamino)-cyclopropyl]-phenylethynyl}-benzoate (**Compound 115**, 65.0  
17 mg, 0.16 mmol) in ethanol (3 mL) and tetrahydrofuran (3 mL) was treated  
18 with NaOH (80.0 mg, 2.0 mmols, 2.0 mL of a 1N aqueous solution) and  
19 stirred overnight at room temperature. Work-up afforded 45.0 mg (75%) of  
20 the title compound as a solid.

21 <sup>1</sup>H NMR (d<sub>6</sub>-DMSO) δ: 7.96 (2H, d, J = 8.3 Hz), 7.66 (2H, d, J = 8.3 Hz), 7.58  
22 (2H, d, J = 8.2 Hz), 7.42 (2H, d, J = 8.2 Hz), 7.29-7.18 (5H, m), 3.52 (2H, s),  
23 2.00 (3H, s), 1.02 (2H, m), 0.87 (2H, m).

24 (4-Bromo-2-methyl-phenyl)-methanol (**Intermediate 133**)

25       A solution of methyl 4-bromo-2-methyl-benzoate (1.05 g, 4.58 mmols)  
26 in 10 mL of Et<sub>2</sub>O was cooled to 0 °C and treated with LiAlH<sub>4</sub> (177.0 mg, 4.58  
27 mmols), stirred for 3 hours, and then carefully quenched with H<sub>2</sub>O. The  
28 mixture was extracted with Et<sub>2</sub>O and the combined organic layers were

1 washed with H<sub>2</sub>O and saturated aqueous NaCl, dried (MgSO<sub>4</sub>), and  
2 concentrated under reduced pressure. The title compound, 830.0 mg (90%),  
3 was isolated by column chromatography (10-30% EtOAc-hexanes) as a  
4 colorless oil.

5 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.30 (2H, m), 7.18 (1H, d, J = 8.8 Hz), 4.57 (2H, d, J =  
6 5.5 Hz), 2.27 (3H, s), 2.13 (1H, t, J = 5.5 Hz).

7 (4-Bromo-2-methyl-benzyloxy)-trimethylsilane (**Intermediate 134**)

8 To a solution of (4-bromo-2-methyl-phenyl)-methanol (**Intermediate**  
9 **133**, 500.0 mg, 2.48 mmols), in 10 mL THF was added triethylamine (374.0  
10 mg, 3.70 mmols) and chlorotrimethylsilane (297.0 mg, 2.70 mmols). The  
11 resulting solution was stirred for 17 hours at 25 °C and then treated with H<sub>2</sub>O  
12 and extracted with Et<sub>2</sub>O. The combined organic layers were washed with H<sub>2</sub>O,  
13 10% aqueous HCl, saturated NaHCO<sub>3</sub>, and saturated NaCl before being dried  
14 (MgSO<sub>4</sub>) and concentrated under reduced pressure. The title compound, 550.0  
15 mg (81%), was isolated by column chromatography (5% EtOAc-hexanes) as a  
16 colorless oil.

17 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.35-7.28 (3H, m), 4.64 (2H, s), 2.29 (3H, s), 0.20 (9H,  
18 s).

19 2-Methyl-4-trimethylsilyl-ethynyl-1-trimethylsilyloxymethyl-benzene  
20 (**Intermediate 135**)

21 Using General Procedure D; (4-bromo-2-methyl-benzyloxy)-  
22 trimethylsilane (**Intermediate 134**, 550.0 mg, 2.01 mmol) in triethylamine (8  
23 mL) was treated with copper(I)iodide (38.0 mg, 0.20 mmol) and then sparged  
24 with argon for 5 minutes. Trimethylsilyl acetylene (1.05 g, 10.6 mmols) was  
25 then added followed by dichlorobis(triphenylphosphine)palladium(II) (142.0  
26 mg, 0.20 mmol). The resulting reaction mixture was heated to 70 °C for 5  
27 days. The title compound (380.0 mg, 65%) was isolated by chromatography  
28 (0 - 2% EtOAc - hexanes) as an orange oil.

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.31 (3H, m), 4.64 (2H, s), 2.24 (3H, s), 0.24 (9H, s), 0.15 (9H, s).

**(4-Ethynyl-2-methyl-phenyl)-methanol (Intermediate 136)**

Using General Procedure E; 2-methyl-4-trimethylsilanylethynyl-1-trimethylsilanyloxymethyl-benzene (**Intermediate 135**, 380.0 mg, 1.30 mmols) in methanol (10 mL) was treated with potassium carbonate (180.0 mg, 1.3 mmol) and stirred overnight at ambient temperature. The crude alkyne was purified by column chromatography (5-20% EtOAc-hexanes) to give 100.0 mg (34%) of the title compound.

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.06 (3H, m), 4.42 (2H, d, J = 5.2 Hz), 2.81 (1H, s), 2.05 (3H, s), 1.59 (1H, t, J = 5.2 Hz).

**Ethyl 4-(4-hydroxymethyl-3-methyl-phenylethynyl)-benzoate (Compound 117, General Formula 6)**

Using General Procedure F; (4-ethynyl-2-methyl-phenyl)-methanol (**Intermediate 136**, 100.0 mg, 0.44 mmol) and ethyl-4-iodo benzoate (**Reagent A**, 125.0 mg, 0.45 mmol) in triethyl amine (4 mL) was treated with copper(I)iodide (29 mg, 0.15 mmol) and sparged with argon for 5 minutes. Dichlorobis(triphenylphosphine)palladium(II) (102 mg, 0.15 mmol) was added and the reaction mixture was stirred overnight at room temperature. Column chromatography (20-40% EtOAc - hexanes) afforded 130.0 mg (99%) of the title compound as an orange solid.

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.98 (2H, d, J = 8.2 Hz), 7.56 (2H, d, J = 8.2 Hz), 7.36 (3H, m), 4.65 (2H, s), 4.36 (2H, q, J = 7.1 Hz), 2.40 (1H, s), 2.30 (3H, s), 1.39 (3H, t, J = 7.1 Hz).

**Ethyl 4-(4-bromomethyl-3-methyl-phenylethynyl)-benzoate (Intermediate 137)**

A solution of ethyl 4-(4-hydroxymethyl-3-methyl-phenylethynyl)-benzoate (**Compound 117**, 130.0 mg, 0.44 mmol) and triphenylphosphine

(150.0 mg, 0.57 mmol) in 5 mL CH<sub>2</sub>Cl<sub>2</sub> was cooled to 0 °C and *N*-bromosuccinimide (101.0 mg, 0.57 mmol) was added in 5 portions over 20 minutes. The solution was warmed to 25 °C and stirred for 17 hours. The reaction was quenched by the addition of dilute aqueous NaHCO<sub>3</sub>. The resulting mixture was extracted with Et<sub>2</sub>O and the combined organic layers were washed with H<sub>2</sub>O and saturated aqueous NaCl before being dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated under reduced pressure. The title compound, 120.0 mg (76%), was isolated by column chromatography (2-5% EtOAc-hexanes) as a colorless solid.

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 8.01 (2H, d, J = 8.1 Hz), 7.56 (2H, d, J = 8.1 Hz), 7.32 (3H, m), 4.48 (2H, s), 4.38 (2H, q, J = 7.1 Hz), 2.40 (3H, s), 1.39 (3H, t, J = 7.1 Hz).

Ethyl 4-(4-imidazol-1-yl-methyl-3-methyl-phenylethynyl)-benzoate  
(Compound 118, General Formula 6)

A solution of imidazole (30.0 mg, 0.44 mmol) in 2 mL DMF was treated with NaH (11.0 mg, 0.44 mmol) and heated to 90 °C. After 1 h a solution of ethyl 4-(4-bromomethyl-3-methyl-phenylethynyl)-benzoate (Intermediate 137, 120.0 mg, 0.34 mmol) in 2 mL DMF was added and stirring at 90 °C continued for 1 hour. The solution was cooled to room temperature and concentrated under reduced pressure. The title compound, 90.0 mg (71%) was isolated by column chromatography (20-100% EtOAc-hexanes) as a colorless solid.

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 8.02 (2H, d, J = 8.5 Hz), 7.57 (2H, d, J = 8.5 Hz), 7.51 (1H, s), 7.40 (1H, s), 7.36 (1H, dd, J = 1.2, 7.9 Hz), 7.10 (1H, s), 6.93 (1H, d, J = 7.9 Hz), 6.88 (1H, t, J = 1.7 Hz), 5.12 (2H, s), 4.38 (2H, q, J = 7.1 Hz), 2.27 (3H, s), 1.40 (3H, t, J = 7.1 Hz).

4-(4-Imidazol-1-yl-methyl-3-methyl-phenylethynyl)-benzoic acid  
(Compound 119, General Formula 6)

1       Using General Procedure I; a solution of ethyl 4-(4-imidazol-1-  
2 ylmethyl-3-methyl-phenylethynyl)-benzoate (**Compound 118**, 82.0 mg, 0.24  
3 mmol) in ethanol (3 mL) and tetrahydrofuran (3 mL) was treated with NaOH  
4 (120.0 mg, 3.0 mmols, 3.0 mL of a 1N aqueous solution) and stirred overnight  
5 at room temperature. Work-up afforded 51.0 mg (68%) of the title compound  
6 as a solid.

7 <sup>1</sup>H NMR (d<sub>6</sub>-DMSO) δ: 9.20 (1H, s), 7.97 (2H, d, J = 8.2 Hz), 7.73 (2H, m),  
8 7.65 (2H, d, J = 8.2 Hz), 7.52 (1H, s), 7.46 (1H, d, J = 7.9 Hz), 7.13 (1H, d, J =  
9 7.9 Hz), 5.50 (2H, s), 2.32 (3H, s).

10 4-Bromo-1-bromomethyl-2-methyl-benzene (**Intermediate 138**)

11       A solution of (4-bromo-2-methyl-phenyl)-methanol (**Intermediate 133**,  
12 319.0 mg, 1.58 mmol) and triphenylphosphine (466.0 mg, 1.74 mmol) in 5 mL  
13 CH<sub>2</sub>Cl<sub>2</sub> was cooled to 0 °C and *N*-bromosuccinimide (309.0 mg, 1.74 mmol)  
14 was added in 5 portions over 20 minutes. The solution was warmed to 25 °C  
15 and stirred for 17 hours. The reaction was quenched by the addition of dilute  
16 aqueous NaHCO<sub>3</sub>. The resulting mixture was extracted with Et<sub>2</sub>O and the  
17 combined organic layers were washed with H<sub>2</sub>O and saturated aqueous NaCl  
18 before being dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated under reduced pressure. The  
19 title compound, 350.0 mg (84%), was isolated by column chromatography (2-  
20 3% EtOAc-hexanes) as a colorless oil.

21 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.32 (1H, d, J = 2.0 Hz), 7.29 (1H, dd, J = 2.0, 7.9 Hz),  
22 7.15 (1H, d, J = 7.9 Hz), 4.43 (2H, s), 2.37 (3H, s).

23 1-(4-Bromo-2-methyl-benzyl)-1*H*-imidazole (**Intermediate 139**)

24       A solution of imidazole (58.0 mg, 0.86 mmol) in 3 mL DMF was  
25 treated with NaH (20.0 mg, 0.86 mmol) and heated to 90 °C. After 1h a  
26 solution of 4-bromo-1-bromomethyl-2-methyl-benzene (**Intermediate 138**,  
27 190.0 mg, 0.72 mmol) in 3 mL DMF was added and stirring at 90 °C  
28 continued for 1 hour. The solution was cooled to room temperature and

1 concentrated under reduced pressure. The title compound, 160.0 mg (88%)  
2 was isolated by column chromatography (5% MeOH-EtOAc) as a colorless  
3 solid.  
4 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.46 (1H, s), 7.34 (1H, dd, J = 1.8 Hz), 7.30 (1H, dd, J =  
5 1.8, 8.2 Hz), 7.08 (1H, t, J = 1.2 Hz), 6.83 (1H, t, J = 1.2 Hz), 6.80 (1H, d, J =  
6 8.2 Hz), 5.03 (2H, s), 2.23 (3H, s).

7 1-(2-Methyl-4-trimethylsilanylethynyl-benzyl)-1H-imidazole (**Intermediate**  
8 **140**)

9       Using General Procedure D; 1-(4-bromo-2-methyl-benzyl)-1H-  
10 imidazole (**Intermediate 139**, 160.0 mg, 0.64 mmol) in triethylamine (8 mL)  
11 was treated with copper(I)iodide (12.0 mg, 0.07 mmol) and then sparged with  
12 argon for 5 minutes. Trimethylsilyl acetylene (0.70 g, 0.71 mmols) was then  
13 added followed by dichlorobis(triphenylphosphine)palladium(II) (45.0 mg,  
14 0.07 mmol). The resulting reaction mixture was heated to 70 °C for 5 days.  
15 The title compound (140.0 mg, 82%) was isolated by chromatography (5%  
16 MeOH-EtOAc ) as an orange oil.  
17 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.53 (1H, s), 7.38 (1H, s), 7.34 (1H, d, J = 8.0 Hz), 7.15  
18 (1H, s), 6.94 (1H, s), 6.91 (1H, d, J = 8.0 Hz), 5.14 (2H, s), 2.29 (3H, s), 0.31  
19 (9H, s).

20 1-(4-Ethynyl-2-methyl-benzyl)-1H-imidazole (**Intermediate 141**)

21       Using General Procedure E; 1-(2-methyl-4-trimethylsilanylethynyl-  
22 benzyl)-1H-imidazole (**Intermediate 140**, 140.0 mg, 0.53 mmols) in methanol  
23 (5 mL) was treated with potassium carbonate (100.0 mg, 0.72 mmol) and  
24 stirred overnight at ambient temperature. The crude alkyne (105 mg, 100%)  
25 was used directly in the next reaction.  
26 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.49 (1H, s), 7.35 (1H, s), 7.31 (1H, dd, J = 1.7, 7.9 Hz),  
27 7.10 (1H, s), 6.69 (1H, d, J = 7.9 Hz), 6.85 (1H, t, J = 1.2 Hz), 5.14 (2H, s),  
28 3.08 (1H, s), 2.26 (3H, s).



1 Methyl [4-(4-imidazol-1-yl-methyl-3-methyl-phenylethynyl)-phenyl]-acetate  
2 **(Compound 120, General Formula 6)**

3       Using General Procedure F; 1-(4-ethynyl-2-methyl-benzyl)-1*H*-  
4 imidazole (**Intermediate 141**, 101.0 mg, 0.53 mmol) and methyl-(4-  
5 iodophenyl)-acetate (**Reagent B**, 145.0 mg, 0.53 mmol) in triethylamine (5  
6 mL) was treated with copper(I)iodide (34.0 mg, 0.18 mmol) and sparged with  
7 argon for 5 minutes. Dichlorobis(triphenylphosphine)palladium(II) (124 mg,  
8 0.18 mmol) was added and the reaction mixture was stirred overnight at room  
9 temperature. Column chromatography (5% MeOH-EtOAc) afforded 45.0 mg  
10 (25%) of the title compound as an orange oil.

11 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.47 (3H, m), 7.35 (3H, m), 7.27 (3H, m), 6.91 (1H, d, J =  
12 7.3 Hz), 5.11 (2H, s), 3.70 (3H, s), 3.64 (2H, s), 2.26 (3H, s).

13 [4-(4-Imidazol-1-yl-methyl-3-methyl-phenylethynyl)-phenyl]-acetic acid  
14 **(Compound 121, General Formula 6)**

15       Using General Procedure I; a solution of methyl [4-(4-imidazol-1-  
16 ylmethyl-3-methyl-phenylethynyl)-phenyl]-acetate (**Compound 120**, 45.0 mg,  
17 0.13 mmol) in ethanol (2 mL) and tetrahydrofuran (2 mL) was treated with  
18 NaOH (80.0 mg, 2.0 mmols, 2.0 mL of a 1N aqueous solution) and stirred  
19 overnight at room temperature. Work-up afforded 30.0 mg (70%) of the title  
20 compound as a pale-orange solid.

21 <sup>1</sup>H NMR (d<sub>4</sub>-MeOH) δ: 8.97 (1H, s), 7.60 (2H, d J = 8.8 Hz), 7.47 (3H, m),  
22 7.41 (1H, d, J = 7.9 Hz), 7.30 (2H, d, J = 7.9 Hz), 7.23 (1H, d, J = 7.9 Hz),  
23 5.51 (2H, s), 3.64 (2H, s), 2.33 (3H, s).

24 1-Isopropyl-3-methoxy-benzene (Intermediate 142)

25       To a solution of 3-isopropyl-phenol (5.00 g, 36.2 mmols) in 50 mL of  
26 acetone was added K<sub>2</sub>CO<sub>3</sub> (7.50 g, 54.3 mmols) and iodomethane (10.3 g, 72.5  
27 mmols). The resulting solution was heated to 50 °C and stirred for 18 hours,  
28 cooled to room temperature, and concentrated under reduced pressure. The

1 residual oil was dissolved in Et<sub>2</sub>O and washed with H<sub>2</sub>O, saturated aqueous  
2 NaHCO<sub>3</sub>, and saturated aqueous NaCl before being dried (MgSO<sub>4</sub>) and  
3 concentrated under reduced pressure. The crude methyl ether was used  
4 without further purification.

5 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.22 (1H, t, J = 8.1 Hz), 6.84-6.72 (3H, m), 3.81 (3H, s),  
6 2.88 (1H, septet, J = 7.0 Hz), 1.25 (6H, d, J = 7.0 Hz).

7 1-Bromo-2-isopropyl-4-methoxy-benzene (Intermediate 143)

8 A mixture of 1-isopropyl-3-methoxy-benzene (**Intermediate 142**, 3.50  
9 g, 23.3 mmols), molecular sieves, and silica gel in 150 mL CCl<sub>4</sub> was treated  
10 with *N*-bromosuccinimide (4.98 g, 28.0 mmols) at 35 °C for 18 hours. An  
11 additional portion of *N*-bromosuccinimide (830.0 mg, 4.46 mmols) was added  
12 and stirring continued for 6 hours. The mixture was cooled to room  
13 temperature, H<sub>2</sub>O was added, and the mixture was filtered to remove the  
14 solids. The mixture was extracted with Et<sub>2</sub>O and the combined organic layers  
15 were washed with 10% aqueous HCl, H<sub>2</sub>O, saturated aqueous NaHCO<sub>3</sub>, and  
16 saturated NaCl before being dried (MgSO<sub>4</sub>) and concentrated under reduced  
17 pressure. Column chromatography (2.5% EtOAc-hexanes) afforded 4.34 g  
18 (81%) of the title compound as a pale-yellow oil.

19 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.41 (1H, d, J = 8.8 Hz), 6.82 (1H, d, J = 2.6 Hz), 6.61  
20 (1H, dd, J = 2.6, 8.8 Hz), 3.79 (3H, s), 3.31 (1H, septet, J = 6.7 Hz), 1.23 (6H,  
21 d, J = 6.7 Hz).

22 4-Bromo-3-isopropyl-phenol (Intermediate 144)

23 To a solution of 1-bromo-2-isopropyl-4-methoxy-benzene  
24 (**Intermediate 143**, 2.20 g, 9.60 mmols) in 50 mL CH<sub>2</sub>Cl<sub>2</sub> at -78 °C was added  
25 BBr<sub>3</sub> (4.81 g, 19.2 mmols; 19.2 mL of a 1M solution in CH<sub>2</sub>Cl<sub>2</sub>). After stirring  
26 for 3 hours at -78 °C the solution was warmed to 0 °C for 3 hours and then at  
27 25 °C for 1 hour before being quenched with H<sub>2</sub>O. The mixture was diluted  
28 with Et<sub>2</sub>O and washed with H<sub>2</sub>O and saturated aqueous NaCl, dried (Na<sub>2</sub>SO<sub>4</sub>)

1 and concentrated under reduced pressure. Column chromatography (2.5-10%  
2 EtOAc-hexanes) afforded the title compound as a colorless oil.  
3 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.38 (1H, d, J = 8.5 Hz), 6.79 (1H, d, J = 2.9 Hz), 6.57  
4 (1H, dd, J = 2.9, 8.5 Hz), 3.31 (1H, septet, J = 7.0 Hz), 1.22 (6H, d, J = 7.0  
5 Hz).

6 (4-Bromo-3-isopropyl-phenoxy)-tert-butyl-dimethyl-silane (**Intermediate**  
7 **145**)

8 A solution of 4-bromo-3-isopropyl-phenol (**Intermediate 144**, 1.13 g,  
9 5.25 mmols), chloro-tert-butyl-dimethylsilane (0.95 g, 6.30 mmols), and  
10 imidazole (428.0 mg, 6.3 mmols) in 10 mL DMF was stirred at 25 °C for 3  
11 hours. The solution was diluted with H<sub>2</sub>O and extracted with Et<sub>2</sub>O and the  
12 combined organic layers were washed with H<sub>2</sub>O, saturated aqueous NaCl, and  
13 dried (MgSO<sub>4</sub>) before being concentrated under reduced pressure. Column  
14 chromatography (1-2% EtOAc-hexanes) afforded 1.50 g (87%) of the title  
15 compound as a colorless oil.

16 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.32 (1H, d, J = 8.8 Hz), 6.73 (1H, d, J = 3.0 Hz), 6.52  
17 (1H, dd, J = 3.0, 8.8 Hz), 3.26 (1H, septet, J = 6.7 Hz), 1.19 (6H, d, J = 6.7  
18 Hz), 0.96 (9H, s), 0.17 (6H, s).

19 4-(Tert-butyl-dimethyl-silanyloxy)-2-isopropyl-benzaldehyde (**Intermediate**  
20 **146**)

21 A solution of (4-bromo-3-isopropyl-phenoxy)-tert-butyl-dimethyl-  
22 silane (**Intermediate 145**, 1.03 g, 3.13 mmols) in 25 mL E<sub>2</sub>O was cooled to -  
23 78 °C and treated with tert-butyllithium (401.0 mg, 6.26 mmols; 3.7 mL of a  
24 1.7M solution in pentane). After 30 minutes the reaction was quenched with  
25 DMF (913.0 mg, 12.5 mmols) and warmed to room temperature. The solution  
26 was diluted with H<sub>2</sub>O, extracted with Et<sub>2</sub>O and the combined organic layers  
27 washed with H<sub>2</sub>O and saturated aqueous NaCl before being dried (MgSO<sub>4</sub>) and  
28 concentrated under reduced pressure. Column chromatography (2% EtOAc-

1 hexanes) afforded 480.0 mg (55%) of the title compound as a colorless oil.  
2 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 10.19 (1H, s), 7.72 (1H, d, J = 8.5 Hz), 6.85 (1H, d, J =  
3 2.3 Hz), 6.77 (1H, dd, J = 2.3, 8.5 Hz), 3.97 (1H, septet, J = 6.7 Hz), 1.27 (6H,  
4 d, J = 6.7 Hz), 1.00 (9H, s), 0.25 (6H, s).

5 4-Hydroxy-2-isopropyl-benzaldehyde (Intermediate 147)

6 To a solution of 4-(*tert*-butyl-dimethyl-silanyloxy)-2-isopropyl-  
7 benzaldehyde (**Intermediate 146**, 880.0 mg, 3.17 mmols) in 6 mL THF at 0  
8 °C was added tetrabutylammonium fluoride (1.66 g, 6.33 mmols; 6.3 mL of a  
9 1M solution in THF). The pale-yellow solution was stirred for 30 minutes and  
10 quenched by the addition of ice cold H<sub>2</sub>O. The mixture was extracted with  
11 Et<sub>2</sub>O and the combined organic layers were washed with H<sub>2</sub>O and saturated  
12 aqueous NaCl before being dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated under reduced  
13 pressure. Column chromatography (20% EtOAc-hexanes) afforded 500.0 mg  
14 (96%) of the title compound as a colorless solid.

15 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 10.15 (1H, s), 7.79 (1H, d, J = 8.5 Hz), 6.95 (1H, d, J =  
16 2.3 Hz), 6.86 (1H, dd, J = 2.3, 8.5 Hz), 3.96 (1H, septet, J = 6.7 Hz), 1.29 (6H,  
17 d, J = 6.7 Hz).

18 4-Formyl-3-isopropyl-phenyl 1,1,1-trifluoro-methansulfonate (Intermediate  
19 **148)**

20 A solution of 4-hydroxy-2-isopropyl-benzaldehyde (**Intermediate 147**,  
21 300.0 mg, 1.83 mmol) in 10 mL of CH<sub>2</sub>Cl<sub>2</sub> was cooled to 0 °C and to it was  
22 added 2-[N,N-bis(trifluoromethylsulfonyl)amino]-5-chloropyridine (754.0 mg,  
23 1.92 mmol) and triethylamine (592.0 mg, 5.85 mmols). The resulting solution  
24 was warmed to room temperature and stirred for 4.5 hours. The reaction was  
25 quenched by the addition of H<sub>2</sub>O and the mixture extracted with EtOAc and  
26 the combined organic layers were washed with 10% aqueous HCl, saturated  
27 aqueous NaHCO<sub>3</sub>, H<sub>2</sub>O, and saturated aqueous NaCl. The solution was dried  
28 (MgSO<sub>4</sub>) and concentrated under reduced pressure. The title compound was

1 isolated by column chromatography (5-10% EtOAc-hexanes) as a colorless  
2 oil, 470.0 mg (87%).  
3 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 10.37 (1H, s), 7.94 (1H, d, J = 8.5 Hz), 7.33 (1H, d, J =  
4 2.3 Hz), 7.26 (1H, dd, J = 2.3, 8.5 Hz), 4.00 (1H, septet, J = 6.7 Hz), 1.33 (6H,  
5 d, J = 6.7 Hz),

6 4-Hydroxymethyl-3-isopropyl-phenyl 1,1,1-trifluoro-methansulfonate  
7 **(Intermediate 149)**

8 To a solution of 4-formyl-3-isopropyl-phenyl 1,1,1-trifluoro-  
9 methansulfonate (**Intermediate 148**, 540.0 mg, 1.82 mmols) in 7 mL MeOH  
10 at 0 °C was added NaBH<sub>4</sub> (72.0 mg, 1.91 mmols). After stirring 2 hours at 0  
11 °C the reaction was carefully quenched with H<sub>2</sub>O and extracted with Et<sub>2</sub>O.  
12 The combined organic layers were washed with H<sub>2</sub>O and saturated aqueous  
13 NaCl, dried (MgSO<sub>4</sub>), and concentrated under reduced pressure. The title  
14 compound was isolated by column chromatography (5-10% EtOAc-hexanes)  
15 as a colorless oil, 355.0 mg (90%).  
16 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.45 (1H, d, J = 8.5 Hz), 7.17 (1H, d, J = 2.7 Hz), 7.08  
17 (1H, dd, J = 2.7, 8.5 Hz), 4.74 (2H, d, J = 5.3 Hz), 3.21 (1H, septet, J = 7.0  
18 Hz), 2.12 (1H, t, J = 5.3 Hz), 1.24 (6H, d, J = 7.0 Hz).

19 4-(*Tert*-butyl-dimethyl-silanyloxymethyl)-3-isopropyl-phenyl 1,1,1-trifluoro-  
20 methansulfonate (**Intermediate 150**)

21 A solution of 4-hydroxymethyl-3-isopropyl-phenyl 1,1,1-trifluoro-  
22 methansulfonate (**Intermediate 149**, 760.0 mg, 2.55 mmols), chloro-*tert*-  
23 butyl-dimethylsilane (470.0 mg, 3.18 mmols), and imidazole (225.0 mg, 3.25  
24 mmols) in 6 mL DMF was stirred at 25 °C for 17 hours. The solution was  
25 diluted with H<sub>2</sub>O and extracted with Et<sub>2</sub>O and the combined organic layers  
26 were washed with 10% aqueous HCl, saturated aqueous NaHCO<sub>3</sub>, H<sub>2</sub>O, and  
27 saturated aqueous NaCl, and dried (MgSO<sub>4</sub>) before being concentrated under  
28 reduced pressure. Column chromatography (2-5% EtOAc-hexanes) afforded

1 970.0 mg (92%) of the title compound as a colorless oil.

2 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.49 (1H, d, J = 8.5 Hz), 7.10 (1H, d, J = 2.3 Hz), 7.06  
3 (1H, dd, J = 2.3, 8.5 Hz), 4.75 (2H, s), 3.10 (1H, septet, J = 6.7 Hz), 1.21 (6H,  
4 d, J = 6.7 Hz), 0.93 (9H, s), 0.10 (6H, s).

5 1-(*Tert*-butyl-dimethyl-silanyloxymethyl)-2-isopropyl-4-  
6 trimethylsilanylethynyl-benzene (Intermediate 151)

7 To a solution of 4-(*tert*-butyl-dimethyl-silanyloxymethyl)-3-isopropyl-  
8 phenyl 1,1,1-trifluoro-methanesulfonate (**Intermediate 150**, 970.0 mg, 2.35  
9 mmols) in triethylamine (2 mL) and 6 mL DMF was sparged with argon for 15  
10 minutes. Trimethylsilyl acetylene (1.00 g, 10.6 mmols) was then added  
11 followed by dichlorobis(triphenylphosphine)palladium(II) (66.0 mg, 0.09  
12 mmol). The resulting reaction mixture was heated to 95 °C for 20 hours. The  
13 solution was cooled to room temperature and concentrated under reduced  
14 pressure. The title compound (200.0 mg, 78%) was isolated by  
15 chromatography (0-25% EtOAc-hexanes) as an orange oil.

16 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.37-7.25 (3H, m), 4.75 (2H, s), 3.08 (1H, septet, J = 7.0  
17 Hz), 1.21 (6H, d, J = 7.0 Hz), 0.92 (9H, s), 0.25 (9H, s), 0.09 (6H, s).

18 *Tert*-butyl-(4-ethynyl-2-isopropyl-benzyloxy)-dimethyl-silane (Intermediate  
19 152)

20 Using General Procedure E; 1-(*tert*-butyl-dimethyl-silanyloxymethyl)-  
21 2-isopropyl-4-trimethylsilanylethynyl-benzene (**Intermediate 151**, 850.0 mg,  
22 2.36 mmols) in methanol (25 mL) was treated with potassium carbonate  
23 (250.0 mg, 1.81 mmols) and stirred overnight at ambient temperature. The  
24 crude alkyne (650 mg, 95%) was used directly in the next reaction.

25 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.41-7.25 (3H, m), 4.77 (2H, s), 3.07 (1H, septet, J = 7.0  
26 Hz), 3.05 (1H, s), 1.22 (6H, d, J = 7.0 Hz), 0.94 (9H, s), 0.11 (6H, s).

27 Ethyl 4-[4-(*tert*-butyl-dimethyl-silanyloxymethyl)-3-isopropyl-  
28 phenylethynyl]-benzoate (Intermediate 153)

1       Using General procedure F; *tert*-butyl-(4-ethynyl-2-isopropyl-  
2 benzyloxy)-dimethyl-silane (**Intermediate 152**, 300.0 mg, 1.04 mmols) and  
3 ethyl-4-iodo benzoate (**Reagent A**, 287.0 mg, 1.04 mmols) in triethylamine  
4 (8mL) was treated with copper(I)iodide (50.0 mg, 0.26 mmol) and sparged  
5 with argon for 5 minutes. Dichlorobis(triphenylphosphine)palladium(II) (182  
6 mg, 0.26 mmol) was added and the reaction mixture was stirred overnight at  
7 room temperature. Column chromatography (2-4% EtOAc - hexanes)  
8 afforded 310.0 mg (68%) of the title compound as an orange solid. .  
9 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 8.03 (2H, d, J = 8.5 Hz), 7.60 (2H, d, J = 8.5 Hz), 7.48-  
10 7.37 (3H, m), 4.80 (2H, s), 4.39 (2H, q, J = 7.1 Hz), 3.14 (1H, septet, J = 6.8  
11 Hz), 1.40 (3H, t, J = 7.1 Hz), 1.27 (6H, d, J = 6.8 Hz), 0.96 (9H, s), 0.12 (6H,  
12 s).

13 Methyl {4-[4-(*tert*-butyl-dimethyl-silanyloxymethyl)-3-isopropyl-  
14 phenylethynyl]-phenyl}-acetate (**Intermediate 154**)

15       Using General Procedure F; *tert*-butyl-(4-ethynyl-2-isopropyl-  
16 benzyloxy)-dimethyl-silane (**Intermediate 152**, 355.0 mg, 1.26 mmols) and  
17 methyl-(4-iodophenyl)-acetate (**Reagent B**, 349.0 mg, 1.26 mmols) in  
18 triethylamine (8 mL) was treated with copper(I)iodide (60.0 mg, 0.32 mmol)  
19 and sparged with argon for 5 minutes.  
20 Dichlorobis(triphenylphosphine)palladium(II) (222 mg, 0.32 mmol) was added  
21 and the reaction mixture was stirred overnight at room temperature. Column  
22 chromatography (2-5% EtOAc-hexanes) afforded 288.0 mg (66%) of the title  
23 compound as an orange oil.  
24 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.49 (2H, d, J = 8.5 Hz), 7.43-7.35 (3H, m), 7.25 (2H, d, J  
25 = 8.5 Hz), 4.77 (2H, s), 3.69 (3H, s), 3.63 (2H, s), 3.11 (1H, septet, J = 6.7  
26 Hz), 1.25 (6H, d, J = 6.7 Hz), 0.94 (9H, s), 0.10 (6H, s).  
27 Ethyl [4-(4-hydroxymethyl-3-isopropyl-phenylethynyl)-benzoate  
28 (**Compound 122, General Formula 6**)

1 To a solution of ethyl 4-[4-(*tert*-butyl-dimethyl-silanyloxymethyl)-3-  
2 isopropyl-phenylethynyl]-benzoate (**Intermediate 153**, 310.0 mg, 0.71 mmol)  
3 in 4 mL THF at 0 °C was added tetrabutylammonium fluoride (371.0 mg, 1.42  
4 mmols; 1.4 mL of a 1M solution in THF). The pale-yellow solution was  
5 stirred for 10 minutes and quenched by the addition of ice cold H<sub>2</sub>O. The  
6 mixture was extracted with Et<sub>2</sub>O and the combined organic layers were  
7 washed with H<sub>2</sub>O and saturated aqueous NaCl before being dried (Na<sub>2</sub>SO<sub>4</sub>)  
8 and concentrated under reduced pressure. Column chromatography (20-30%  
9 EtOAc-hexanes) afforded 200.0 mg (87%) of the title compound as a colorless  
10 solid.

11 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.98 (2H, d, J = 8.5 Hz), 7.58 (2H, d, J = 8.5 Hz), 7.48  
12 (1H, s), 7.35 (2H, m), 4.71 (2H, s), 4.35 (2H, q, J = 7.1 Hz), 3.19 (1H, septet, J  
13 = 7.0 Hz), 2.51 (1H, s), 1.39 (3H, t, J = 7.1 Hz), 1.25 (6H, d, J = 7.0 Hz).

14 Methyl [4-(4-hydroxymethyl-3-isopropyl-phenylethynyl)-phenyl]-acetate  
15 (**Compound 123**, General Formula 6)

16 To a solution of methyl {4-[4-(*tert*-butyl-dimethyl-silanyloxymethyl)-  
17 3-isopropyl-phenylethynyl]-phenyl}-acetate (**Intermediate 154**, 288.0 mg,  
18 0.66 mmol) in 5 mL THF at 0 °C was added tetrabutylammonium fluoride  
19 (471.0 mg, 1.80 mmols; 1.8 mL of a 1M solution in THF). The pale-yellow  
20 solution was stirred for 15 minutes and quenched by the addition of ice cold  
21 H<sub>2</sub>O. The mixture was extracted with Et<sub>2</sub>O and the combined organic layers  
22 were washed with H<sub>2</sub>O and saturated aqueous NaCl before being dried  
23 (Na<sub>2</sub>SO<sub>4</sub>) and concentrated under reduced pressure. Column chromatography  
24 (5-10% EtOAc-hexanes) afforded 180.0 mg (85%) of the title compound as a  
25 colorless solid.

26 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.48 (3H, m), 7.32 (2H, m), 7.24 (2H, d, J = 8.5 Hz), 4.69  
27 (2H, s), 3.68 (3H, s), 3.62 (2H, s), 3.18 (1H, septet, J = 7.0 Hz), 2.21 (1H, s),  
28 1.25 (6H, d, J = 7.0 Hz).



1 Ethyl [4-(4-bromomethyl-3-isopropyl-phenylethynyl)-benzoate

2 **(Intermediate 155)**

3       A solution of ethyl [4-(4-hydroxymethyl-3-isopropyl-phenylethynyl)-  
4 benzoate (**Compound 122**, 200.0 mg, 0.62 mmol) and triphenylphosphine  
5 (211.0 mg, 0.81 mmol) in 5 mL CH<sub>2</sub>Cl<sub>2</sub> was cooled to 0 °C and *N*-  
6 bromosuccinimide (144.0 mg, 0.81 mmol) was added in 5 portions over 20  
7 minutes. The solution was warmed to 25 °C and stirred for 17 hours. The  
8 reaction was quenched by the addition of dilute aqueous NaHCO<sub>3</sub>. The  
9 resulting mixture was extracted with Et<sub>2</sub>O and the combined organic layers  
10 were washed with H<sub>2</sub>O and saturated aqueous NaCl before being dried  
11 (Na<sub>2</sub>SO<sub>4</sub>) and concentrated under reduced pressure. The title compound, 220.0  
12 mg (93%), was isolated by column chromatography (5% EtOAc-hexanes) as a  
13 pale-yellow solid.

14 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 8.03 (2H, d, J = 8.2 Hz), 7.59 (2H, d, J = 8.2 Hz), 7.48  
15 (1H, s), 7.31 (2H, m), 4.55 (2H, s), 4.39 (2H, q, J = 7.1 Hz), 3.29 (1H, septet, J  
16 = 7.0 Hz), 1.40 (3H, t, J = 7.1 Hz), 1.30 (6H, d, J = 7.0 Hz).

17 Methyl [4-(4-bromomethyl-3-isopropyl-phenylethynyl)-phenyl]-acetate

18 **(Intermediate 156)**

19       A solution of methyl [4-(4-hydroxymethyl-3-isopropyl-  
20 phenylethynyl)-phenyl]-acetate (**Compound 123**, 180.0 mg, 0.56 mmol) and  
21 triphenylphosphine (190.0 mg, 0.73 mmol) in 5 mL CH<sub>2</sub>Cl<sub>2</sub> was cooled to 0  
22 °C and *N*-bromosuccinimide (130.0 mg, 0.73 mmol) was added in 5 portions  
23 over 20 minutes. The solution was warmed to 25 °C and stirred for 17 hours.  
24 The reaction was quenched by the addition of dilute aqueous NaHCO<sub>3</sub>. The  
25 resulting mixture was extracted with Et<sub>2</sub>O and the combined organic layers  
26 were washed with H<sub>2</sub>O and saturated aqueous NaCl before being dried  
27 (Na<sub>2</sub>SO<sub>4</sub>) and concentrated under reduced pressure. The title compound, 212.0  
28 mg (98%), was isolated by column chromatography (5-10% EtOAc-hexanes)

1 as a pale-yellow oil.

2 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.48 (3H, m), 7.28 (4H, m), 4.55 (2H, s), 3.69 (3H, s),  
3 3.63 (2H, s), 3.28 (1H, septet, J = 7.0 Hz), 1.30 (6H, d, J = 7.0 Hz).

4 Ethyl [4-(4-imidazol-1-yl-methyl-3-isopropyl-phenylethynyl)-phenyl]-  
5 benzoate (**Compound 124, General Formula 6**)

6 A solution of ethyl [4-(4-bromomethyl-3-isopropyl-phenylethynyl)-  
7 benzoate (**Intermediate 155**, 120.0 mg, 0.31 mmol) and 1-acetylimidazole  
8 (36.0 mg, 0.33 mmol) in 5 mL CH<sub>3</sub>CN was heated at 65 °C for 4 hours and  
9 then at 55 °C for 16 hours. The solution was cooled to room temperature,  
10 diluted with H<sub>2</sub>O and made basic by addition of Na<sub>2</sub>CO<sub>3</sub>, and extracted with  
11 EtOAc. The combined organic layers were washed with H<sub>2</sub>O and saturated  
12 aqueous NaCl, dried (MgSO<sub>4</sub>), and concentrated under reduced pressure.  
13 Column chromatography (1% Et<sub>3</sub>N in 5% MeOH-EtOAc) afforded 75.0 mg  
14 (65%) of the title compound as a colorless solid.

15 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 8.03 (2H, d, J = 8.5 Hz), 7.60 (2H, d, J = 8.5 Hz), 7.53  
16 (1H, d, J = 1.5 Hz), 7.49 (1H, s), 7.35 (1H, dd, J = 1.5, 7.9 Hz), 7.09 (1H, bs),  
17 6.98 (1H, d, J = 7.9 Hz), 6.85 (1H, bs), 5.19 (2H, s), 4.39 (2H, q, J = 7.1 Hz),  
18 3.08 (1H, septet, J = 6.8 Hz), 1.40 (3H, t, J = 7.1 Hz), 1.20 (6H, d, J = 6.8 Hz).

19 Methyl [4-(4-imidazol-1-yl-methyl-3-isopropyl-phenylethynyl)-phenyl]-  
20 acetate (**Compound 125, General Formula 6**)

21 A solution of methyl [4-(4-bromomethyl-3-isopropyl-phenylethynyl)-  
22 phenyl]-acetate (**Intermediate 156**, 72.0 mg, 0.19 mmol) and 1-  
23 acetylimidazole (22.0 mg, 0.20 mmol) in 5 mL CH<sub>3</sub>CN was heated at 65 °C  
24 for 8h and then at 55 °C for 16 hours. The solution was cooled to room  
25 temperature, diluted with H<sub>2</sub>O and made basic by addition of Na<sub>2</sub>CO<sub>3</sub>, and  
26 extracted with EtOAc. The combined organic layers were washed with H<sub>2</sub>O  
27 and saturated aqueous NaCl, dried (MgSO<sub>4</sub>), and concentrated under reduced  
28 pressure. Column chromatography (0.5% Et<sub>3</sub>N in 5% MeOH-EtOAc) afforded

1 40.0 mg (58%) of the title compound as a colorless solid.

2 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.49 (4H, m), 7.33 (1H, dd, J = 1.5, 7.9 Hz), 7.28 (2H, d,  
3 J = 8.5 Hz), 7.08 (1H, t, J = 1.2 Hz), 6.95 (1H, d, J = 7.9 Hz), 6.84 (1H, t, J =  
4 1.2 Hz), 5.17 (2H, s), 3.70 (3H, s), 3.64 (2H, s), 3.06 (1H, septet, J = 6.8 Hz),  
5 1.20 (6H, d, J = 6.8 Hz).

6 [4-(4-Imidazol-1-yl-methyl-3-isopropyl-phenylethynyl)-phenyl]-benzoic acid  
7 (Compound 126, General Formula 6)

8 Using General Procedure I; a solution of ethyl [4-(4-imidazol-1-  
9 ylmethyl-3-isopropyl-phenylethynyl)-phenyl]-benzoate (Compound 124, 75.0  
10 mg, 0.20 mmol) in ethanol (4 mL) and tetrahydrofuran (1 mL) was treated  
11 with NaOH (120.0 mg, 3.0 mmols, 3.0 mL of a 1N aqueous solution) and  
12 stirred overnight at room temperature. Work-up afforded 68.0 mg (88%) of  
13 the title compound as a colorless solid.

14 <sup>1</sup>H NMR (d<sub>4</sub>-MeOH) δ: 9.01 (1H, s), 8.01 (2H, d, J = 8.2 Hz), 7.63-7.57 (5H,  
15 m), 7.44 (1H, d, J = 7.9 Hz), 7.29 (1H, d, J = 7.9 Hz), 5.59 (2H, s), 3.17 (1H,  
16 septet, J = 6.8 Hz), 1.20 (6H, d, J = 6.8 Hz).

17 [4-(4-Imidazol-1-yl-methyl-3-isopropyl-phenylethynyl)-phenyl]-acetic acid  
18 (Compound 127, General Formula 6)

19 Using General Procedure I; a solution of methyl [4-(4-imidazol-1-  
20 ylmethyl-3-isopropyl-phenylethynyl)-phenyl]-acetate (Compound 125, 40.0  
21 mg, 0.11 mmol) in ethanol (4 mL) and tetrahydrofuran (1 mL) was treated  
22 with NaOH (120.0 mg, 3.0 mmols, 3.0 mL of a 1N aqueous solution) and  
23 stirred overnight at room temperature. Work-up afforded 22.0 mg (52%) of  
24 the title compound as a colorless solid.

25 <sup>1</sup>H NMR (d<sub>4</sub>-MeOH) δ: 9.02 (1H, bs), 7.62 (1H, t, J = 1.4 Hz), 7.58 (2H, m),  
26 7.49 (2H, d, J = 8.2 Hz), 7.43 (1H, dd, J = 1.5, 7.9 Hz), 7.31 (3H, m), 5.58  
27 (2H, s), 3.68 (2H, s), 3.16 (1H, septet, J = 6.7 Hz), 1.18 (6H, d, J = 6.7 Hz).

28 4-Bromo-N-cyclopropyl-2-methyl-benzamide (Intermediate 157)

1        A solution of 4-bromo-2-methylbenzoic acid and  $\text{SOCl}_2$  was refluxed  
2 for 3 hours, cooled to room temperature and concentrated under reduced  
3 pressure. The residue was dissolved in 30 mL  $\text{CH}_2\text{Cl}_2$  and combined with  
4 cyclopropyl amine (810.0 mg, 14.3 mmols) and pyridine (2.05 g, 26.0 mmols).  
5 The solution was stirred for 18 hours and then diluted with EtOAc before  
6 being washed with 5% aqueous HCl, saturated  $\text{NaHCO}_3$ , and saturated  
7 aqueous NaCl. The solution was dried ( $\text{MgSO}_4$ ) and concentrated under  
8 reduced pressure leaving the title compound as a colorless solid.  
9  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 7.34 (1H, d,  $J = 2.3$  Hz), 7.28 (1H, dd,  $J = 2.3, 8.2$  Hz),  
10 7.13 (1H, d,  $J = 8.2$  Hz), 6.10 (1H, bs), 2.85 (1H, m), 2.37 (3H, s), 0.85 (2H,  
11 m), 0.59 (2H, m).

12 (4-Bromo-2-methyl-benzyl)-cyclopropyl-amine (Intermediate 158)

13        To a solution of 4-bromo-*N*-cyclopropyl-2-methyl-benzamide  
14 (**Intermediate 157**, 1.81 g, 7.12 mmols) in THF (12 mL) was added  
15  $\text{BH}_3 \cdot \text{SMe}_2$  (1.08 g, 14.24 mmols). The solution was heated to 60 °C for 6  
16 hours, cooled to room temperature and carefully treated with saturated  
17 aqueous  $\text{Na}_2\text{CO}_3$  (30 mL) and stirred for 17 hours. This mixture was extracted  
18 with EtOAc and the combined organic layers were washed with  $\text{H}_2\text{O}$ , saturated  
19 aqueous NaCl before being dried ( $\text{MgSO}_4$ ) and concentrated under reduced  
20 pressure. The title compound was isolated by column chromatography (10-  
21 15% EtOAc-hexanes).

22  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 7.26 (2H, m), 7.12 (1H, d,  $J = 7.9$  Hz), 3.76 (2H, s), 2.31  
23 (3H, s), 2.14 (1H, m), 0.44 (2H, m), 0.36 (2H, m).

24 (4-Bromo-2-methyl-benzyl)-cyclopropyl-ethyl-amine (Intermediate 159)

25        A mixture of (4-bromo-2-methyl-benzyl)-cyclopropyl-amine  
26 (**Intermediate 158**, 600.0 mg, 2.49 mmols), ethyl iodide (1.56 g, 10.0 mmols),  
27 and  $\text{K}_2\text{CO}_3$  (690.0 mg, 5.00 mmols) in 10 mL acetone was heated at 60 °C for  
28 18 hours. The mixture was cooled to room temperature, diluted with  $\text{H}_2\text{O}$ , and

1 extracted with EtOAc. The combined organic layers were washed with H<sub>2</sub>O  
2 and saturated aqueous NaCl before being dried (MgSO<sub>4</sub>) and concentrated  
3 under reduced pressure. The title compound was isolated by column  
4 chromatography (2.5% EtOAc-hexanes).  
5 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.23 (2H, m), 7.12 (1H, d, J = 7.6 Hz), 3.62 (2H, s), 2.56  
6 (2H, q, J = 7.3 Hz), 2.29 (3H, s), 1.75 (1H, m), 1.04 (3H, t, J = 7.3 Hz), 0.39  
7 (2H, m), 0.30 (2H, m).

8 Cyclopropyl-ethyl-(2-methyl-4-trimethylsilanylethynyl-benzyl)-amine  
9 (**Intermediate 160**)

10 Using General Procedure D; (4-bromo-2-methyl-benzyl)-cyclopropyl-  
11 ethyl-amine (**Intermediate 159**, 620.0 mg, 2.31 mmols) in triethylamine (8  
12 mL) was treated with copper(I)iodide (44.0 mg, 0.23 mmol) and then sparged  
13 with argon for 15 minutes. Trimethylsilylacetylene (1.04 g, 10.6 mmols) was  
14 then added followed by dichlorobis-(triphenylphosphine)palladium(II) (162.0  
15 mg, 0.23 mmol). The resulting reaction mixture was heated to 70 °C for 5  
16 days. The title compound (650.0 mg, 98%) was isolated by chromatography  
17 (1-4% EtOAc - hexanes).  
18 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.32 (1H, s), 7.20 (2H, m), 3.65 (2H, s), 2.55 (2H, q, J =  
19 7.3 Hz), 2.28 (3H, s), 1.74 (1H, m), 1.03 (3H, t, J = 7.3 Hz), 0.36 (2H, m), 0.27  
20 (2H, m), 0.24 (9H, s).

21 Cyclopropyl-ethyl-(4-ethynyl-2-methyl-benzyl)-amine (**Intermediate 161**)

22 Using General Procedure E; cyclopropyl-ethyl-(2-methyl-4-  
23 trimethylsilanylethynyl-benzyl)-amine (**Intermediate 160**, 650.0 mg, 2.30  
24 mmols) in methanol (10mL) was treated with potassium carbonate (100.0 mg,  
25 0.72 mmol) and stirred overnight at ambient temperature. The crude alkyne  
26 (495 mg, 99%) was used directly in the next reaction.  
27 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.32 (1H, s), 7.21 (2H, m), 3.66 (2H, s), 3.01 (1H, s), 2.56  
28 (2H, q, J = 7.3 Hz), 2.29 (3H, s), 1.76 (1H, m), 1.04 (3H, t, J = 7.3 Hz), 0.40

1 (2H, m), 0.29 (2H, m).

2 Ethyl 4-{4-[(cyclopropyl-ethyl-amino)-methyl]-3-methyl-phenylethynyl}-  
3 benzoate (**Compound 128, General Formula 6**)

4 Using General Procedure F; cyclopropyl-ethyl-(4-ethynyl-2-methyl-  
5 benzyl)-amine (**Intermediate 161**, 190.0 mg, 0.89 mmol) and ethyl-4-iodo  
6 benzoate (**Reagent A**, 245.0 mg, 0.89 mmol) in triethylamine (5 mL) was  
7 treated with copper(I)iodide (56.0 mg, 0.30 mmol) and sparged with argon for  
8 15 minutes. Dichlorobis(triphenylphosphine)-palladium(II) (208 mg, 0.30  
9 mmol) was added and the reaction mixture was stirred overnight at room  
10 temperature. Column chromatography (3-5% EtOAc - hexanes) afforded the  
11 title compound.

12 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 8.01 (2H, d, J = 8.2 Hz), 7.56 (2H, d, J = 8.2 Hz), 7.31-  
13 7.24 (3H, m), 4.38 (2H, q, J = 7.1 Hz), 3.68 (2H, s), 2.58 (2H, q, J = 7.3 Hz),  
14 2.32 (3H, s), 1.77 (1H, m), 1.39 (3H, t, J = 7.1 Hz), 1.05 (3H, t, J = 7.3 Hz),  
15 0.39 (2H, m), 0.31 (2H, m).

16 Methyl (4-{4-[(cyclopropyl-ethyl-amino)-methyl]-3-methyl-phenylethynyl}-  
17 phenyl)-acetate (**Compound 129, General Formula 6**)

18 Using General Procedure F; cyclopropyl-ethyl-(4-ethynyl-2-methyl-  
19 benzyl)-amine (**Intermediate 161**, 300.0 mg, 1.41 mmols) and methyl-(4-  
20 iodophenyl)-acetate (**Reagent B**, 388.0 mg, 1.41 mmols) in triethylamine (8  
21 mL) was treated with copper(I)iodide (67.0 mg, 0.35 mmol) and sparged with  
22 argon for 15 minutes. Dichlorobis(triphenylphosphine)palladium(II) (246 mg,  
23 0.35 mmol) was added and the reaction mixture was stirred overnight at room  
24 temperature. Column chromatography (5-7% EtOAc - hexanes) afforded  
25 270.0 mg (53%) of the title compound as a pale-yellow oil.

26 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.47 (2H, d, J = 7.9 Hz), 7.30-7.22 (5H, m), 3.70 (3H, s),  
27 3.68 (2H, s), 3.63 (2H, s), 2.58 (2H, q, J = 7.3 Hz), 2.32 (3H, s), 1.77 (1H, m),  
28 1.05 (3H, t, J = 7.3 Hz), 0.39 (2H, m), 0.30 (2H, m).

1 4-{4-[(Cyclopropyl-ethyl-amino)-methyl]-3-methyl-phenylethynyl}-benzoic  
2 acid: (Compound 130, General Formula 6)

3 Using General Procedure I; a solution of ethyl 4-{4-[(cyclopropyl-  
4 ethyl-amino)-methyl]-3-methyl-phenylethynyl}-benzoate (**Compound 128**,  
5 130.0 mg, 0.36 mmol) in ethanol (5 mL) and tetrahydrofuran (5 mL) was  
6 treated with NaOH (360.0 mg, 9.0 mmols, 3.0 mL of a 3N aqueous solution)  
7 and stirred overnight at room temperature. Work-up afforded 115.0 mg (96%)  
8 of the title compound as a colorless solid.

9 <sup>1</sup>H NMR (d<sub>6</sub>-acetone) δ: 8.05 (2H, d, J = 8.2 Hz), 7.64 (2H, d, J = 8.2 Hz),  
10 7.32 (3H, m), 3.73 (2H, s), 2.59 (2H, q, J = 7.3 Hz), 2.35 (3H, s), 1.83 (1H, m),  
11 1.05 (3H, t, J = 7.3 Hz), 0.38 (2H, m), 0.27 (2H, m).

12 (4-{4-[(Cyclopropyl-ethyl-amino)-methyl]-3-methyl-phenylethynyl}-phenyl)-  
13 acetic acid (Compound 131, General Formula 6)

14 Using General Procedure I; a solution of methyl (4-{4-[(cyclopropyl-  
15 ethyl-amino)-methyl]-3-methyl-phenylethynyl}-phenyl)-acetate (**Compound**  
16 **129**, 140.0 mg, 0.39 mmol) in ethanol (5 mL) and tetrahydrofuran (5 mL) was  
17 treated with NaOH (360.0 mg, 9.0 mmols, 3.0 mL of a 3N aqueous solution)  
18 and stirred overnight at room temperature. Work-up followed by HPLC  
19 (Partisil-10 pac 10% H<sub>2</sub>O-CH<sub>3</sub>CN) afforded the title compound.

20 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.45 (2H, d, J = 8.2 Hz), 7.25 (5H, m), 4.16 (2H, m), 3.82  
21 (2H, s), 3.56 (2H, s), 2.75 (2H, q, J = 7.3 Hz), 2.30 (3H, s), 1.86 (1H, m), 1.14  
22 (3H, t, J = 7.3 Hz), 0.54 (2H, m), 0.46 (2H, m).

23 Ethyl {4-(4-cyclopropylaminomethyl-3-isopropyl-phenylethynyl)-benzoate  
24 (Compound 132, General Formula 6)

25 A solution of ethyl [4-(4-bromomethyl-3-isopropyl-phenylethynyl)-  
26 benzoate (**Intermediate 155**, 110.0 mg, 0.29 mmol) and cyclopropylamine  
27 (420.0 mg, 7.4 mmols) in EtOH (5 mL) was stirred at 25 °C for 6 hours and  
28 then concentrated under reduced pressure. The residue was dissolved in

1 EtOAc and washed with saturated aqueous NaHCO<sub>3</sub>, H<sub>2</sub>O and saturated  
2 aqueous NaCl. The solution was dried (MgSO<sub>4</sub>) and concentrated under  
3 reduced pressure to give 103 mg (99%) of the title compound as an orange oil.  
4 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 8.01 (2H, d, J = 8.5 Hz), 7.59 (2H, d, J = 8.5 Hz), 7.47  
5 (1H, s), 7.30 (2H, m), 4.38 (2H, q, J = 7.1 Hz), 3.89 (2H, s), 3.26 (1H, septet, J  
6 = 7.0 Hz), 2.17 (1H, m), 1.40 (3H, t, J = 7.1 Hz), 1.26 (6H, d, J = 7.0 Hz), 0.45  
7 (2H, m), 0.39 (2H, m).

8 Ethyl 4-{4-[(cyclopropyl-ethyl-amino)-methyl]-3-isopropyl-phenylethynyl}-  
9 benzoate (**Compound 133, General Formula 6**)

10 To a solution of ethyl {4-(4-cyclopropylaminomethyl-3-isopropyl-  
11 phenylethynyl)-benzoate (**Compound 132**, 103.0 mg, 0.29 mmol) in 6 mL of  
12 acetone was added ethyl iodide (67.0 mg, 0.43 mmol) and K<sub>2</sub>CO<sub>3</sub> (79.0 mg,  
13 0.57 mmol). The mixture was stirred at 60 °C for 6 hours, cooled to room  
14 temperature and quenched by the addition of H<sub>2</sub>O. The mixture was extracted  
15 with EtOAc and the combined organic layers were washed with H<sub>2</sub>O and  
16 saturated aqueous NaCl before being dried (MgSO<sub>4</sub>) and concentrated under  
17 reduced pressure. Column chromatography (4-5% EtOAc - hexanes) afforded  
18 68.0 mg (59%) of the title compound.

19 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 8.01 (2H, d, J = 8.6 Hz), 7.58 (2H, d, J = 8.6 Hz), 7.44  
20 (1H, s), 7.28 (2H, m), 4.39 (2H, q, J = 7.1 Hz), 3.73 (2H, s), 3.55 (1H, septet, J  
21 = 6.6 Hz), 2.57 (2H, q, J = 7.3 Hz), 1.75 (1H, m), 1.40 (3H, t, J = 7.1 Hz), 1.22  
22 (6H, d, J = 6.6 Hz), 1.05 (3H, t, J = 7.3 Hz), 0.37 (2H, m), 0.28 (2H, m).

23 4-{4-[(Cyclopropyl-ethyl-amino)-methyl]-3-isopropyl-phenylethynyl}-  
24 benzoic acid (**Compound 134, General Formula 6**)

25 Using General Procedure I; a solution of ethyl 4-{4-[(cyclopropyl-  
26 ethyl-amino)-methyl]-3-isopropyl-phenylethynyl}-benzoate (**Compound 133**,  
27 68.0 mg, 0.17 mmol) in ethanol (3 mL) and tetrahydrofuran (3 mL) was  
28 treated with NaOH (600.0 mg, 15.0 mmols, 3.0 mL of a 5N aqueous solution)



1 and stirred overnight at room temperature and then at 55 °C for 9 hours.  
2 Work-up followed by crystallization of the solid residue from hot CH<sub>3</sub>CN  
3 afforded 45.0 mg (72%) of the title compound as a pale-yellow solid.  
4 <sup>1</sup>H NMR (d<sub>6</sub>-acetone) δ: 8.05 (2H, d, J = 8.1 Hz), 7.66 (2H, d, J = 8.1 Hz),  
5 7.49 (1H, s), 7.32 (2H, m), 3.78 (2H, s), 3.44 (1H, septet, J = 6.7 Hz), 2.59  
6 (2H, q, J = 7.3 Hz), 1.80 (1H, m), 1.21 (6H, d, J = 6.7 Hz), 1.05 (3H, t, J = 7.3  
7 Hz), 0.40 (2H, m), 0.26 (2H, m).

8 Methyl [4-(8,8-dimethyl-5-oxo-5,6,7,8-tetrahydro-naphthalen-2-yl-ethynyl)-  
9 phenyl]-acetate (Compound 4, General Formula 8)

10 Using General Procedure F; 6-ethynyl-4,4-dimethyl-3,4-dihydro-2H-  
11 naphthalen-1-one (Intermediate 13, 190.0 mg, 0.96 mmol) and methyl-(4-  
12 iodophenyl)-acetate (Reagent B, 245.0 mg, 0.96 mmol) in triethyl amine (8  
13 mL) was treated with copper(I)iodide (46 mg, 0.24 mmol) and sparged with  
14 argon for 15 minutes. Dichlorobis(triphenylphosphine)palladium(II) (168 mg,  
15 0.24 mmol) was added and the reaction mixture was stirred overnight at room  
16 temperature. Column chromatography (10-20% EtOAc - hexanes) afforded  
17 250.0 mg (75%) of the title compound as a pale-yellow solid.  
18 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.99 (1H, d, J = 7.9 Hz), 7.57 (1H, d, J = 1.5 Hz), 7.51  
19 (2H, d, J = 8.5 Hz), 7.43 (1H, dd, J = 1.5, 7.9 Hz), 7.29 (2H, d, J = 8.5 Hz),  
20 3.70 (3H, s), 3.65 (2H, s), 2.73 (2H, t, J = 7.0 Hz), 2.04 (2H, t, J = 7.0 Hz),  
21 1.41 (6H, s).

22 Methyl [4-(5-hydroxy-8,8-dimethyl-5,6,7,8-tetrahydro-naphthalen-2-yl-  
23 ethynyl)-phenyl]-acetate (Compound 135, General Formula 4)

24 To a solution of methyl [4-(8,8-dimethyl-5-oxo-5,6,7,8-tetrahydro-  
25 naphthalen-2-yl-ethynyl)-phenyl]-acetate (Compound 4) in 5 mL MeOH at 0  
26 °C was added NaBH<sub>4</sub> (18.0 mg, 0.48 mmol). The reaction was stirred at 0 °C  
27 for 2 hours and then quenched by the addition of H<sub>2</sub>O. The solution was  
28 diluted with Et<sub>2</sub>O and washed with H<sub>2</sub>O and saturated aqueous NaCl before

1 being dried ( $\text{MgSO}_4$ ) and the solvents were removed under reduced pressure.  
2 Column chromatography (20-40% EtOAc-hexanes) afforded 140.0 mg (87%)  
3 of the title compound as a colorless oil.  
4  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 7.49 (3H, m), 7.39 (1H, d,  $J = 7.9$  Hz), 7.31 (1H, dd,  $J =$   
5 1.5, 7.9 Hz), 7.25 (2H, d,  $J = 8.2$  Hz), 4.58 (1H, bs), 3.68 (3H, s), 3.62 (2H, s),  
6 2.05 (1H, m), 1.79 (2H, m), 1.60 (1H, m), 1.33 (3H, s), 1.26 (3H, s).

7 Methyl [4-(5-imidazol-1-yl)-8,8-dimethyl-5,6,7,8-tetrahydro-naphthalen-2-  
8 ylethynyl]-phenyl]-acetate (Compound 136, General Formula 4)

9 A solution of methyl [4-(5-hydroxy-8,8-dimethyl-5,6,7,8-tetrahydro-  
10 naphthalen-2-ylethynyl)-phenyl]-acetate (Compound 135, 140.0 mg, 0.40  
11 mmol) and carbonyldiimidazole (136.0 mg, 0.84 mmol) in 5 mL THF was  
12 heated to 65 °C for 48 hours. The solution was cooled to room temperature  
13 and concentrated under reduced pressure. The residue was dissolved in  $\text{Et}_2\text{O}$   
14 and washed with 5% aqueous NaOH,  $\text{H}_2\text{O}$ , and saturated aqueous NaCl before  
15 being dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated under reduced pressure. Column  
16 chromatography (5% MeOH- $\text{CH}_2\text{Cl}_2$ ) afforded 50.0 mg (31%) of the title  
17 compound as a colorless solid.

18  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 7.57 (1H, d,  $J = 1.5$  Hz), 7.52-7.45 (3H, m), 7.27 (3H, m),  
19 7.08 (1H, s), 6.81 (2H, m), 5.30 (1H, t,  $J = 5.8$  Hz), 3.71 (3H, s), 3.65 (2H, s),  
20 2.20 (2H, m), 1.75 (2H, m), 1.40 (3H, s), 1.36 (3H, s).

21 [4-(5-Imidazol-1-yl)-8,8-dimethyl-5,6,7,8-tetrahydro-naphthalen-2-yl-ethynyl]-  
22 phenyl]-acetic acid (Compound 137, General Formula 4)

23 Using General Procedure I; a solution of methyl [4-(5-imidazol-1-yl-  
24 8,8-dimethyl-5,6,7,8-tetrahydro-naphthalen-2-yl-ethynyl)-phenyl]-acetate  
25 (Compound 136, 50.0 mg, 0.13 mmol) in ethanol (4 mL) was treated with  
26 NaOH (120.0 mg, 3.0 mmols, 3.0 mL of a 1N aqueous solution) and stirred  
27 overnight at room temperature. Work-up afforded 40.0 mg (83%) of the title  
28 compound as a pale-orange solid.

29  $^1\text{H}$  NMR ( $d_4$ -MeOH)  $\delta$ : 8.93 (1H, s), 7.68 (1H, s), 7.61 (1H, s), 7.54 (1H, s),

1 7.47 (2H, d, J = 8.2 Hz), 7.31 (3H, m), 6.95 (1H, d, J = 8.2 Hz), 5.83 (1H, t, J  
2 = 5.8 Hz), 3.68 (1H, s), 3.63 (1H, s), 2.38 (1H, m), 2.26 (1H, m), 1.76 (2H, m),  
3 1.45 (3H, s), 1.36 (3H, s).

4 Ethyl [4-(5-imidazol-1-yl-8,8-dimethyl-5,6,7,8-tetrahydro-naphthalen-2-yl-  
5 ethynyl)-benzoate (Compound 138, General Formula 4)

6 A solution of ethyl [4-(5-hydroxy-8,8-dimethyl-5,6,7,8-tetrahydro-  
7 naphthalen-2-yl-ethynyl)-benzoate (180.0 mg, 0.52 mmol) and  
8 carbonyldiimidazole (176.0 mg, 1.08 mmol) in 5 mL THF was heated to 65 °C  
9 for 21 hours. The solution was cooled to room temperature and concentrated  
10 under reduced pressure. The residue was dissolved in Et<sub>2</sub>O and washed with  
11 5% aqueous NaOH, H<sub>2</sub>O, and saturated aqueous NaCl before being dried  
12 (Na<sub>2</sub>SO<sub>4</sub>) and concentrated under reduced pressure. Column chromatography  
13 (5% MeOH-CH<sub>2</sub>Cl<sub>2</sub>) afforded 50.0 mg (24%) of the title compound as a  
14 colorless solid.

15 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 8.03 (2H, d, J = 7.9 Hz), 7.59 (3H, m), 7.46 (1H, s), 7.29  
16 (1H, dd, J = 1.5, 8.3 Hz), 7.09 (1H, s), 6.82 (1H, d, J = 8.2 Hz), 6.81 (1H, s),  
17 5.31 (1H, t, J = 5.8 Hz), 4.39 (2H, q, J = 7.1 Hz), 2.20 (2H, m), 1.75 (2H, m),  
18 1.40 (9H, m).

19 [4-(5-Imidazol-1-yl-8,8-dimethyl-5,6,7,8-tetrahydro-naphthalen-2-yl-ethynyl)-  
20 benzoic acid (Compound 139, General Formula 4)

21 Using General Procedure I; a solution of ethyl [4-(5-imidazol-1-yl-8,8-  
22 dimethyl-5,6,7,8-tetrahydro-naphthalen-2-yl-ethynyl)-benzoate (Compound  
23 138, 50.0 mg, 0.13 mmol) in ethanol (3 mL) and tetrahydrofuran (1 mL) was  
24 treated with NaOH (120.0 mg, 3.0 mmols, 3.0 mL of a 1N aqueous solution)  
25 and stirred overnight at room temperature. Work-up afforded 40.0 mg (87%)  
26 of the title compound as a colorless solid.

27 <sup>1</sup>H NMR (d<sub>4</sub>-MeOH) δ: 8.92 (1H, s), 8.04 (2H, d, J = 8.2 Hz), 7.74 (1H, d, J =  
28 1.5 Hz), 7.62 (3H, m), 7.57 (1H, t, J = 1.5 Hz), 7.38 (1H, dd, J = 1.5, 7.9 Hz),  
29 6.97 (1H, d, J = 7.9 Hz), 5.83 (1H, t, J = 5.8 Hz), 2.33 (2H, m), 1.78 (2H, m),

1 1.47 (3H, s), 1.39 (3H, s).

2 2-Isopropyl-4-trifluoromethanesulfonyloxy-benzyl acetate (**Intermediate**  
3 **162**)

4 To a solution of 4-hydroxymethyl-3-isopropylphenyl 1,1,1-  
5 trifluoromethanesulfonate (**Intermediate 149**, 190.0 mg, 0.64 mmol) in 5 mL  
6 CH<sub>2</sub>Cl<sub>2</sub> was added acetyl chloride (75.0 mg, 0.96 mmol) and pyridine (101.0  
7 mg, 1.38 mmols). After stirring for 3 hours at 25 °C the reaction was  
8 quenched by the addition of H<sub>2</sub>O and the resulting mixture extracted with  
9 EtOAc. The combined organic layers were washed with H<sub>2</sub>O and saturated  
10 aqueous NaCl, dried (MgSO<sub>4</sub>) and concentrated under reduced pressure. The  
11 title compound, 182 mg (84%), was isolated from the residual oil by column  
12 chromatography (5 - 10% EtOAc-hexanes) as a colorless oil.  
13 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.43 (1H, d, J = 8.7 Hz), 7.19 (1H, d, J = 2.7 Hz), 7.09  
14 (1H, dd, J = 2.7, 8.5 Hz), 5.17 (2H, s), 3.18 (1H, septet, J = 6.7 Hz), 2.10 (3H,  
15 s), 1.26 (6H, d, J = 6.7 Hz).

16 4-Isopropenyloxymethyl-3-isopropyl-phenyl 1,1,1-trifluoromethanesulfonate  
17 (**Intermediate 163**)

18 Using General Procedure 1; 2-isopropyl-4-  
19 trifluoromethanesulfonyloxy-benzyl acetate (**Intermediate 162**, 182.0 mg,  
20 0.54 mmols), and 1.1 mL of Tebbe's Reagent (159.0 mg, 0.56 mmols) afforded  
21 130.0 mg (72%) of the title compound as a colorless oil after column  
22 chromatography (2-5% EtOAc-hexanes).  
23 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.43 (1H, d, J = 8.5 Hz), 7.18 (1H, d, J = 2.6 Hz), 7.09  
24 (1H, dd, J = 2.6, 8.5 Hz), 4.75 (2H, s), 3.98 (2H, s), 3.12 (1H, septet, J = 6.7  
25 Hz), 1.88 (3H, s), 1.25 (6H, d, J = Hz).

26 3-Isopropyl-4-(1-methyl-cyclopropoxymethyl)-phenyl 1,1,1-  
27 trifluoromethanesulfonate (**Intermediate 164**)

28 Using General Procedure 2; 4-isopropenyloxymethyl-3-isopropylphenyl

1 1,1,1-trifluoromethanesulfonate (**Intermediate 163**, 130.0 mg, 0.39 mmol),  
2 Et<sub>2</sub>Zn (272.0 mg, 2.2 mmols), and CH<sub>2</sub>I<sub>2</sub> (702.0 mg, 2.6 mmols) in 3.0 mL  
3 Et<sub>2</sub>O afforded 120.0 mg (89%) of the title compound as a colorless oil after  
4 column chromatography (4-5% EtOAc - hexanes).  
5 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.39 (1H, d, J = 8.5 Hz), 7.13 (1H, d, J = 2.7 Hz), 7.05  
6 (1H, dd, J = 2.7, 8.5 Hz), 4.54 (2H, s), 3.16 (1H, septet, J = 6.7 Hz), 1.47 (3H,  
7 s), 1.24 (6H, d, J = 6.7 Hz), 0.86 (2H, m), 0.48 (2H, m).

8 [3-Isopropyl-4-(1-methyl-cyclopropoxymethyl)-phenylethynyl]-  
9 trimethylsilane (**Intermediate 165**)

10 Using General Procedure D; 3-isopropyl-4-(1-methyl-  
11 cyclopropoxymethyl)-phenyl 1,1,1-trifluoromethanesulfonate (**Intermediate**  
12 **164**, 120.0 mg, 0.34mmol) in triethylamine (2 mL) and anhydrous DMF (5  
13 mL) was sparged with argon for 5 minutes. Trimethylsilyl acetylene (700.0  
14 mg, 0.71 mmol) was then added followed by  
15 dichlorobis(triphenylphosphine)palladium(II) (24.0 mg, 0.03 mmol). The  
16 resulting reaction mixture was heated to 95 °C for 60 hours. The title  
17 compound 110.0 mg, (99%) was isolated by chromatography (0-1% EtOAc -  
18 hexanes).  
19 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.36 (1H, s), 7.24 (2H, bs), 4.53 (2H, s), 3.11 (1H, septet,  
20 J = 6.7 Hz), 1.45 (3H, s), 1.22 (6H, d, J = 6.7 Hz), 0.85 (2H, m), 0.44 (2H, m),  
21 0.25 (9H, s).

22 4-Ethynyl-2-isopropyl-1-(1-methyl-cyclopropoxymethyl)-benzene  
23 (**Intermediate 166**)

24 Using General Procedure E; [3-isopropyl-4-(1-methyl-  
25 cyclopropoxymethyl)-phenylethynyl]-trimethylsilane (**Intermediate 165**,  
26 110.0 mg, 0.37 mmol) in methanol (6 mL) was treated with potassium  
27 carbonate (80.0 mg, 0.58 mmol) and stirred overnight at ambient temperature.  
28 The crude alkyne (84 mg, 100%) was used directly in the next reaction.

1 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.55 (1H, s), 7.41 (2H, m), 4.68 (2H, s), 3.26 (1H, septet,  
2 J = 6.8 Hz), 3.18 (1H, s), 1.60 (3H, s), 1.37 (6H, d, J = 6.8 Hz), 0.99 (2H, m),  
3 0.59 (2H, m).

4 Methyl {4-[3-isopropyl-4-(1-methyl-cyclopropoxymethyl)-phenylethynyl]-  
5 phenyl}-acetate (Compound 140, General Formula 6)

6 Using General Procedure F; 4-ethynyl-2-isopropyl-1-(1-methyl-  
7 cyclopropoxymethyl)-benzene (Intermediate 166, 78.0 mg, 0.34 mmol) and  
8 methyl-(4-iodophenyl)-acetate (Reagent B, 94.0 mg, 0.34 mmol) in  
9 triethylamine (8 mL) was treated with copper(I)iodide (22.0 mg, 0.11 mmol)  
10 and sparged with argon for 5 minutes.  
11 Dichlorobis(triphenylphosphine)palladium(II) (79 mg, 0.11 mmol) was added  
12 and the reaction mixture was stirred at room temperature for 3.5 hours.  
13 Column chromatography (2-5% EtOAc - hexanes) afforded 77.0 mg (60%) of  
14 the title compound as a yellow oil.

15 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.49 (2H, d, J = 8.2 Hz), 7.43 (1H, d, J = 1.5 Hz), 7.33-  
16 7.24 (4H, m), 4.55 (2H, s), 3.70 (3H, s), 3.63 (2H, s), 3.14 (1H, septet, J = 6.8  
17 Hz), 1.47 (3H, s), 1.25 (6H, d, J = 6.8 Hz), 0.86 (2H, m), 0.46 (2H, m).

18 {4-[3-Isopropyl-4-(1-methyl-cyclopropoxymethyl)-phenylethynyl]-phenyl}-  
19 acetic acid (Compound 141, Formula 6)

20 Using General Procedure I; a solution methyl {4-[3-isopropyl-4-(1-  
21 methyl-cyclopropoxymethyl)-phenylethynyl]-phenyl}-acetate (Compound  
22 140, 70.0 mg, 0.19 mmol) in ethanol (3 mL) and tetrahydrofuran (3 mL) was  
23 treated with NaOH (240.0 mg, 6.0 mmols, 2.0 mL of a 3N aqueous solution)  
24 and stirred overnight at room temperature. Work-up and purification by  
25 HPLC (Partisil 10-pac, 10% H<sub>2</sub>O/CH<sub>3</sub>CN) afforded of the title compound as a  
26 colorless solid.

27 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.50 (2H, d, J = 8.2 Hz), 7.43 (1H, s), 7.33-7.24 (4H, m),  
28 4.55 (2H, s), 3.65 (2H, s), 3.14 (1H, septet, J = 6.7 Hz), 1.47 (3H, s), 1.25 (6H,

1 d,  $J = 6.7$  Hz), 0.87 (2H, m), 0.46 (2H, m).

2 2,6-Di-*tert*-butyl-4-trimethylsilanylethynyl-phenol: (**Intermediate 167**)

3 Following General Procedure D and using 4-bromo-2,6-di-*t*-butyl-  
4 phenol (1.43g, 5mmol), triethyl amine (15mL), anhydrous tetrahydrofuran  
5 (15mL), copper(I)iodide (0.06g, 0.31mmol), trimethylsilyl acetylene (4.9g,  
6 50mmol) and dichlorobis(triphenylphosphine)palladium(II) (0.18g, 0.26mmol)  
7 followed by flash column chromatography over silica gel (230-400 mesh)  
8 using hexane as eluent, the title compound was obtained (1.35g, 90%).

9  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.29 (s, 2H), 5.35 (s, 1H), 1.42 (s, 18H), 0.24  
10 (s, 9H).

11 (3,5-Di-*tert*-butyl-4-methoxy-phenylethynyl)-trimethyl-silane: (**Intermediate**  
12 **168**)

13 A solution 2,6-di-*tert*-butyl-4-trimethylsilanylethynyl-phenol  
14 (**Intermediate 167**, 0.302g, 1mmol) in acetone (5mL) was treated with  
15 potassium carbonate (0.138g, 1mmol) and methyl iodide (0.142g, 1mmol) and  
16 stirred overnight at room temperature. The volatiles were distilled off *in*  
17 *vacuo* and the residue was purified by flash column chromatography on silica  
18 gel (230-400 mesh) using ethyl acetate as the eluent to afford the title  
19 compound as a white solid (0.28g, 90%).

20  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.41 (s, 2H), 3.70 (s, 3H), 1.49 (s, 18H), 0.30  
21 (s, 9H).

22 1,3-Di-*tert*-butyl-5-ethynyl-2-methoxy-benzene: (**Intermediate 169**)

23 Following General Procedure E and (3,5-di-*tert*-butyl-4-methoxy-  
24 phenylethynyl)-trimethyl-silane (**Intermediate 168**, 0.28g, 0.9mmol),  
25 potassium carbonate (0.98g, 7.1mmol) and methanol (10mL) followed by flash  
26 column chromatography over silica gel (230-400 mesh) using hexane as the  
27 eluent, the title compound was obtained (0.23g, 100%).

28  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.46 (s, 2H), 3.75 (s, 3H), 3.05 (s, 1H), 1.49 (s,

1 18H).

2 [4-(3,5-Di-*tert*-butyl-4-methoxy-phenylethynyl)-phenyl]-acetic acid methyl  
3 ester: (Compound 142, General Formula 5)

4 Following General Procedure F and using 1,3-di-*tert*-butyl-5-ethynyl-2-  
5 methoxy-benzene (**Intermediate 169**, 0.094g, 0.36mmol), methyl-4-iodo  
6 phenyl acetate (**Reagent B**, 0.09g, 0.32mmol), triethyl amine (5mL),  
7 anhydrous tetrahydrofuran (5mL), copper(I)iodide (0.02g, 0.1mmol) and  
8 dichlorobis(triphenylphosphine)palladium(II) (0.06g, 0.085mmol) followed by  
9 flash column chromatography over silica gel (230-400 mesh) using 10 % ethyl  
10 acetate in hexane as the eluent, the title compound (0.114g, 81%) was obtained  
11 as an oil.

12 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.52 (d, 2H, *J* = 8.0Hz), 7.46 (s, 2H), 7.28 (d,  
13 2H, *J* = 8.2Hz), 3.72 (s, 3H), 3.71(s, 3H), 3.66 (s, 2H), 1.47 (s, 18H).

14 [4-(3,5-Di-*tert*-butyl-4-methoxy-phenylethynyl)-phenyl]-acetic acid:  
15 **(Compound 143, General Formula 5)**

16 Following General Procedure I and using [4-(3,5-di-*tert*-butyl-4-  
17 methoxy-phenylethynyl)-phenyl]-acetic acid methyl ester (**Compound 142**,  
18 0.114g, 0.29mmol), 5M aqueous sodium hydroxide solution (2mL) and  
19 ethanol (4mL), followed by preparative reverse phase HPLC using 10% water  
20 in acetonitrile as the mobile phase, the title compound was obtained as a white  
21 solid (0.097g, 88%).

22 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.55(d, 2H, *J* = 8.0Hz), 7.48 (s, 2H), 7.30 (d,  
23 2H, *J* = 8.2Hz), 3.74 (s, 3H), 3.69 (s, 2H), 1.49 (s, 18H).

24 [4-(3,5-Di-*tert*-butyl-4-methoxy-phenylethynyl)-2-fluoro-phenyl]-acetic acid  
25 methyl ester: (Compound 144, General Formula 5)

26 Following General Procedure F and using 1,3-di-*tert*-butyl-5-ethynyl-2-  
27 methoxy-benzene (**Intermediate 169**, 0.087g, 0.33mmol), methyl-2-fluoro-4-  
28 iodo phenyl acetate (**Reagent H**, 0.088g, 0.30mmol), triethyl amine (5mL),  
29 anhydrous tetrahydrofuran (10mL), copper(I)iodide (0.02g, 0.1mmol) and  
30 dichlorobis(triphenylphosphine)palladium(II) (0.06g, 0.085mmol) followed by



1 flash column chromatography over silica gel (230-400 mesh) using 10 % ethyl  
2 acetate in hexane as the eluent, the title compound (0.122g, 89%) was  
3 obtained.

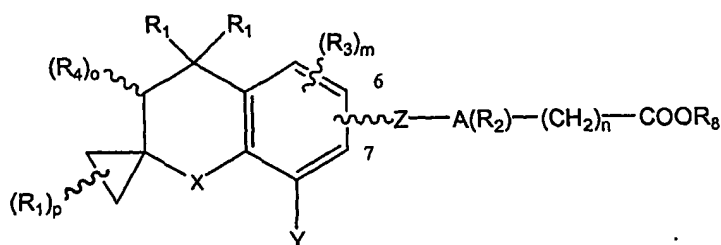
4 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.46 (s, 2H), 7.33-7.24 (m, 3H), 3.75 (s, 3H),  
5 3.73(s, 3H), 3.72 (s, 2H), 1.48 (s, 18H).

6 [4-(3,5-Di-*tert*-butyl-4-methoxy-phenylethynyl)-2-fluoro-phenyl]-acetic acid:  
7 **(Compound 145, General Formula 5)**

8 Following General Procedure I and using [4-(3,5-di-*tert*-butyl-4-  
9 methoxy-phenylethynyl)-2-fluoro-phenyl]-acetic acid methyl ester  
10 **(Compound 144, 0.122g, 0.29mmol)**, 5M aqueous sodium hydroxide solution  
11 (1mL) and ethanol (4mL), followed preparative reverse phase HPLC using  
12 10% water in acetonitrile as the mobile phase, the title compound was  
13 obtained as a white solid (0.077g, 65%).  
14 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.42 (s, 2H), 7.29-7.19 (m, 3H), 3.71 (s, 2H),  
15 3.69 (s, 3H), 1.43 (s, 18H).

1 WHAT IS CLAIMED IS:

2 1. A method of inhibiting the enzyme cytochrome P450RAI in a  
3 mammal by administering to said mammal an effective dose of a  
4 pharmaceutical composition comprising a compound of the formula



12 wherein A is a phenyl or naphthyl group, or heteroaryl selected from a  
13 group consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl,  
14 thiazolyl, oxazolyl, imidazolyl and pyrazolyl, said phenyl and heteroaryl  
15 groups being optionally substituted with one or two R<sub>2</sub> groups;

16 X is O, S or NR where R is H, alkyl of 1 to 6 carbons or benzyl;

17 Y is H, alkyl of 1 to 10 carbons, benzyl, lower alkyl or halogen  
18 substituted benzyl, fluoro-substituted alkyl of 1 to 10 carbons, cycloalkyl of 3  
19 to 6 carbons, lower alkyl substituted cycloalkyl of 3 to 6 carbons, Cl, Br, or I;

20 Z is -C≡C-,

21 -(CR<sub>1</sub>=CR<sub>1</sub>)<sub>n</sub>, where n' is an integer having the value 1 - 5,

22 -CO-NR<sub>1</sub>-,

23 NR<sub>1</sub>-CO-,

24 -CO-O-,

25 -O-CO-,

26 -CS-NR<sub>1</sub>-,

27 NR<sub>1</sub>-CS-,

28 -CO-S-,

1               -S-CO-,

2               -N=N-;

3               **R<sub>1</sub>** is independently H or alkyl of 1 to 6 carbons;

4               **p** is an integer having the values of 0 to 4;

5               **R<sub>2</sub>** is independently H, alkyl of 1 to 6 carbons, F, Cl, Br, I, CF<sub>3</sub>, fluoro  
6 substituted alkyl of 1 to 6 carbons, alkoxy of 1 to 6 carbons, or alkylthio of 1  
7 to 6 carbons;

8               **R<sub>3</sub>** is independently alkyl of 1 to 6 carbons, F, Cl, Br, I, fluoro  
9 substituted alkyl of 1 to 6 carbons, OH, SH, alkoxy of 1 to 6 carbons, alkylthio  
10 of 1 to 6 carbons or benzyl;

11              **m** is an integer having the values 0 to 2;

12              **R<sub>4</sub>** is independently H, alkyl of 1 to 6 carbons, or F; fluorosubstituted  
13 alkyl of 1 to 6 carbons, or halogen;

14              **o** is an integer having the values of 0 to 2;

15              **n** is an integer having the values of 0 to 4, and

16              **R<sub>8</sub>** is H, alkyl of 1 to 6 carbons, -CH<sub>2</sub>O(C<sub>1-6</sub>-alkyl), or a cation of a  
17 pharmaceutically acceptable base.

18              2. A method in accordance with Claim 1 wherein the compound has  
19 the formula

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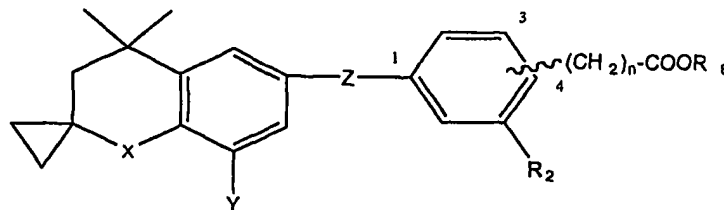
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where **X** is O or CH<sub>3</sub>N;

**Y** is H or cyclopropyl;

1        **Z** is -C≡C- or -CO-O-;

2        **R<sub>2</sub>** is H or F;

3        **n** is 0 or 1, and

4        **R<sub>8</sub>** is H, alkyl of 1 to 6 carbons, or a cation of a pharmaceutically  
5 acceptable base.

6        3. A method in accordance with Claim 2 wherein the compound is  
7 selected from the group consisting of:

8        benzoic acid, 4-[(3,4-dihydro-4,4-dimethylspiro[2*H*-1-benzopyran-2,1'-  
9 cyclopropane]-6-yl)ethynyl]-, benzeneacetic acid, 4-[(3,4-dihydro-4,4-  
10 dimethylspiro[2*H*-1-benzopyran-2,1'-cyclopropane]-6-yl)ethynyl]- and 2-  
11 fluoro-benzoic acid, 4-[(3,4-dihydro-4,4-dimethylspiro[2*H*-1-benzopyran-2,1'-  
12 cyclopropane]-6-yl)ethynyl]- or a salt with a pharmaceutically acceptable  
13 base or a C<sub>1-6</sub> alkyl ester of said compound.

14        4. A method in accordance with Claim 2 wherein the compound is  
15 selected from the group consisting of:

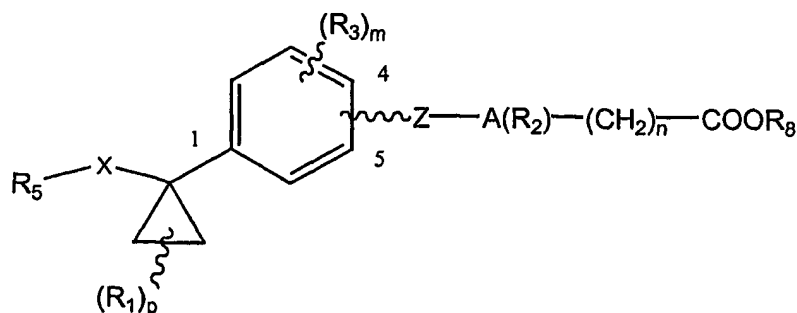
16        benzeneacetic acid, 4-[(8-cyclopropyl-3,4-dihydro-4,4-  
17 dimethylspiro[2*H*-1-benzopyran-2,1'-cyclopropane]-6-yl)ethynyl]-, 4-[(8-  
18 cyclopropyl-3,4-dihydro-4,4-dimethylspiro[2*H*-1-benzopyran-2,1'-  
19 cyclopropane]-6-yl)ethynyl]-2-fluoro-benzeneacetic acid, benzoic acid, 4-[(8-  
20 cyclopropyl-3,4-dihydro-4,4-dimethylspiro[2*H*-1-benzopyran-2,1'-  
21 cyclopropane]-6-yl)ethynyl]- and 4-[(8-cyclopropyl-3,4-dihydro-4,4-  
22 dimethylspiro[2*H*-1-benzopyran-2,1'-cyclopropane]-6-yl)ethynyl]-2-fluoro-  
23 benzoic acid or a salt with a pharmaceutically acceptable base or a C<sub>1-6</sub> alkyl  
24 ester of said compound.

25        5. A method in accordance with Claim 2 wherein the compound is  
26 spiro[2*H*-1-benzopyran-2,1'-cyclopropane]-6-carboxylic acid, 8-cyclopropyl-  
27 3,4-dihydro-4,4-dimethyl-, 4-(carboxymethyl)phenyl ester or a salt with a  
28 pharmaceutically acceptable base or a C<sub>1-6</sub> alkyl ester of said compound.

1           6. A method in accordance with Claim 2 wherein the compound is  
 2 spiro[2*H*-1-benzopyran-2,1'-cyclopropane]-6-carboxylic acid, 8-cyclopropyl-  
 3 3,4-dihydro-4,4-dimethyl-, 3-(carboxymethyl)phenyl ester or a salt with a  
 4 pharmaceutically acceptable base or a C<sub>1-6</sub> alkyl ester of said compound.

5           7. A method in accordance with Claim 2 wherein the compound is  
 6 benzoic acid, 4-[(1,4,4-trimethylspiro[2*H*-1-1,2,3,4-tetrahydroquinoline-2,1'-  
 7 cyclopropane]-6-yl)ethynyl]- or a salt with a pharmaceutically acceptable  
 8 base or a C<sub>1-6</sub> alkyl ester of said compound.

9           8. A method of inhibiting the enzyme cytochrome P450RAI in a  
 10 mammal by administering to said mammal an effective dose of a  
 11 pharmaceutical composition comprising a compound of the formula



20           wherein A is a phenyl or naphthyl group, or heteroaryl selected from a  
 21 group consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl,  
 22 thiazolyl, oxazolyl, imidazolyl and pyrazolyl, said phenyl and heteroaryl  
 23 groups being optionally substituted with one or two R<sub>2</sub> groups;

24           X is O, S or NR where R is H, alkyl of 1 to 6 carbons or benzyl;

25           Z is -C≡C-,

26           -(CR<sub>1</sub>=CR<sub>1</sub>)<sub>n</sub>, where n' is an integer having the value 1 - 5,

27           -CO-NR<sub>1</sub>-,

28           NR<sub>1</sub>-CO-,

1            -CO-O-,

2            -O-CO-,

3            -CS-NR<sub>1</sub>-,

4            NR<sub>1</sub>-CS-,

5            -CO-S-,

6            -S-CO-,

7            -N=N-;

8            R<sub>1</sub> is independently H or alkyl of 1 to 6 carbons;

9            p is an integer having the values of 0 to 4;

10           R<sub>2</sub> is independently H, alkyl of 1 to 6 carbons, F, Cl, Br, I, fluoro  
11 substituted alkyl of 1 to 6 carbons, alkoxy of 1 to 6 carbons, or alkylthio of 1  
12 to 6 carbons;

13           R<sub>3</sub> is independently alkyl of 1 to 6 carbons, F, Cl, Br, I, fluoro  
14 substituted alkyl of 1 to 6 carbons, OH, SH, alkoxy of 1 to 6 carbons, alkylthio  
15 of 1 to 6 carbons or benzyl;

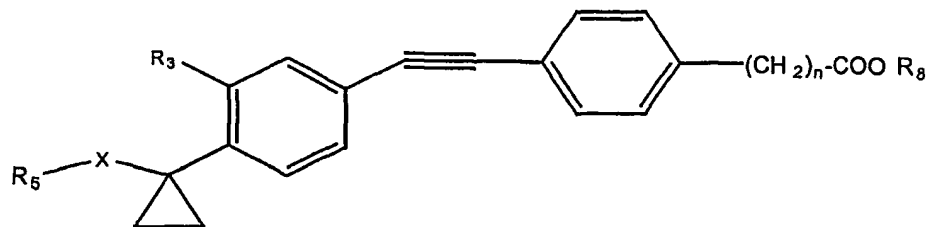
16           m is an integer having the values 0 to 4;

17           R<sub>5</sub> is H, alkyl of 1 to 6 carbons, fluorosubstituted alkyl of 1 to 6  
18 carbons, benzyl, or lower alkyl or halogen substituted benzyl;

19           n is an integer having the values of 0 to 4, and

20           R<sub>8</sub> is H, alkyl of 1 to 6 carbons, -CH<sub>2</sub>O(C<sub>1-6</sub>-alkyl), or a cation of a  
21 pharmaceutically acceptable base.

22           9. A method in accordance with Claim 8 wherein the compound has  
23 the formula



1        where X is O, NR where R is H, *n*-propyl or benzyl;  
2        R<sub>3</sub> is H or lower alkyl of 1 to 6 carbons;  
3        R<sub>5</sub> is benzyl or lower alkyl of 1 to 6 carbons;  
4        *n* is 0 or 1, and  
5        R<sub>8</sub> is H, alkyl of 1 to 6 carbons, or a cation of a pharmaceutically  
6 acceptable base.

7        10. A method in accordance with Claim 9 wherein the compound is  
8 selected from the group consisting of 4-[4-(1-propylamino-cyclopropyl)-  
9 phenylethynyl]-benzoic acid and 4-[4-(1-benzylamino-cyclopropyl)-  
10 phenylethynyl]-benzoic acid or a salt with a pharmaceutically acceptable base  
11 or a C<sub>1-6</sub> alkyl ester of said compound.

12       11. A method in accordance with Claim 9 wherein the compound is  
13 selected from the group consisting of 4-[4-(1-dibenzylamino-cyclopropyl)-  
14 phenylethynyl]-benzoic acid and 4-[4-(1-benzylmethylamino-cyclopropyl)-  
15 phenylethynyl]-benzoic acid or a salt with a pharmaceutically acceptable base  
16 or a C<sub>1-6</sub> alkyl ester of said compound.

17       12. A method in accordance with Claim 9 wherein the compound is  
18 selected from the group consisting of 4-[4-(1-benzyloxycyclopropyl)-  
19 phenylethynyl]-benzoic acid, 4-[4-(1-benzyloxycyclopropyl)-3-methyl-  
20 phenylethynyl]-benzoic acid and 4-[4-(1-benzyloxycyclopropyl)-3-ethyl-  
21 phenylethynyl]-benzoic acid or a salt with a pharmaceutically acceptable  
22 base or a C<sub>1-6</sub> alkyl ester of said compound.

23       13. A method in accordance with Claim 9 wherein the compound is  
24 selected from the group consisting of {4-[4-(1-benzyloxycyclopropyl)-  
25 phenylethynyl]-phenyl}-acetic acid, {4-[4-(1-benzyloxycyclopropyl)-3-  
26 methyl-phenylethynyl]-phenyl}-acetic acid and {4-[4-(1-  
27 benzyloxycyclopropyl)-3-ethyl-phenylethynyl]-phenyl}-acetic acid or a salt  
28 with a pharmaceutically acceptable base or a C<sub>1-6</sub> alkyl ester of said

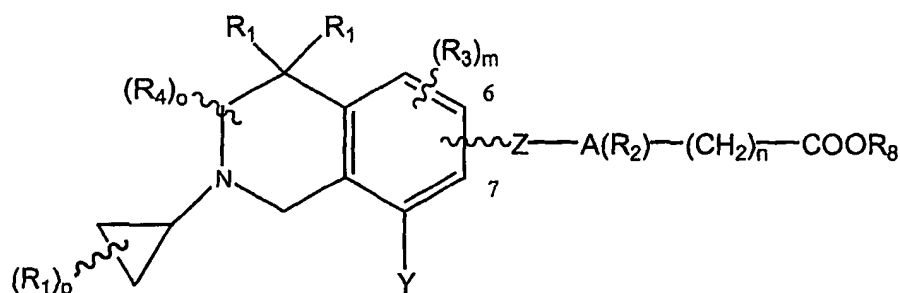
1 compound.

2       **14.** A method in accordance with Claim 9 wherein the compound is  
3 selected from the group consisting of 4-[4-(1-methoxycyclopropyl)-  
4 phenylethynyl]-benzoic acid, 4-[4-(1-isopropoxycyclopropyl)-phenylethynyl]-  
5 benzoic acid, 4-[4-(1-isopropoxycyclopropyl)-3-methyl-phenylethynyl]-  
6 benzoic acid, 4-[4-[1-(2,2-dimethylpropyloxy)-cyclopropyl]-3-methyl-  
7 phenylethynyl]-benzoic acid and 4-[4-(1-ethoxycyclopropyl)-3-*tert*-butyl-  
8 phenylethynyl]-benzoic acid or a salt with a pharmaceutically acceptable  
9 base or a C<sub>1-6</sub> alkyl ester of said compound.

10       **15.** A method in accordance with Claim 9 wherein the compound is  
11 selected from the group consisting of {4-[4-(1-methoxycyclopropyl)-  
12 phenylethynyl]-phenyl}-acetic acid, {4-[4-(1-isopropoxycyclopropyl)-  
13 phenylethynyl]-phenyl}-acetic acid, {4-[4-(1-isopropoxycyclopropyl)-3-  
14 methyl-phenylethynyl]-phenyl}-acetic acid, {4-[4-[1-(2,2-  
15 dimethylpropyloxy)-cyclopropyl]-3-methyl-phenylethynyl]-phenyl}-acetic  
16 acid, {4-[4-(1-benzyloxycyclopropyl)-3-ethyl-phenylethynyl]-phenyl}-acetic  
17 acid, {4-[4-(1-isopropoxycyclopropyl)-3-ethyl-phenylethynyl]-phenyl}-acetic  
18 acid and {4-[4-(1-ethoxycyclopropyl)-3-*tert*-butyl-phenylethynyl]-phenyl}-  
19 acetic acid or a salt with a pharmaceutically acceptable base or a C<sub>1-6</sub> alkyl  
20 ester of said compound.



1        16. A method of inhibiting the enzyme cytochrome P450RAI in a  
 2 mammal by administering to said mammal an effective dose of a  
 3 pharmaceutical composition comprising a compound of the formula



11        wherein A is a phenyl or naphthyl group, or heteroaryl selected from a  
 12 group consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl,  
 13 thiazolyl, oxazolyl, imidazolyl and pyrazolyl, said phenyl and heteroaryl  
 14 groups being optionally substituted with one or two R<sub>2</sub> groups;

15        Y is H, alkyl of 1 to 10 carbons, benzyl, lower alkyl or halogen  
 16 substituted benzyl, fluoro-substituted alkyl of 1 to 10 carbons, cycloalkyl of 3  
 17 to 6 carbons, lower alkyl substituted cycloalkyl of 1 to 6 carbons, Cl, Br, or I;

18        Z is -C≡C-,

19        -(CR<sub>1</sub>=CR<sub>1</sub>)<sub>n</sub>, where n' is an integer having the value 1 - 5,

20        -CO-NR<sub>1</sub>-,

21        NR<sub>1</sub>-CO-,

22        -CO-O-,

23        -O-CO-,

24        -CS-NR<sub>1</sub>-,

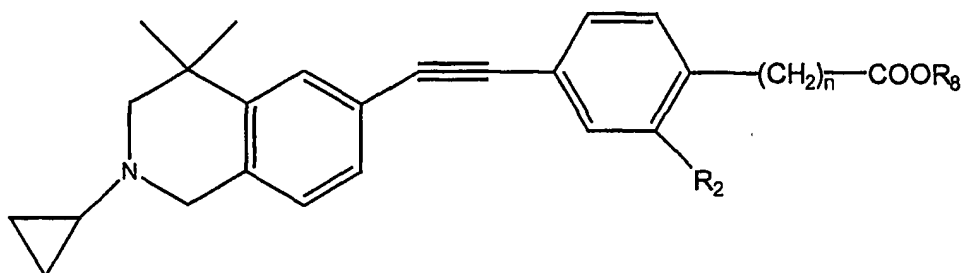
25        NR<sub>1</sub>-CS-,

26        -CO-S-,

27        -S-CO-,

28        -N=N-;

- 1  $R_1$  is independently H or alkyl of 1 to 6 carbons;  
2  $p$  is an integer having the values of 0 to 5;  
3  $R_2$  is independently H, alkyl of 1 to 6 carbons, F, Cl, Br, I, fluoro  
4 substituted alkyl of 1 to 6 carbons, alkoxy of 1 to 6 carbons, or alkylthio of 1  
5 to 6 carbons;  
6  $R_3$  is independently alkyl of 1 to 6 carbons, F, Cl, Br, I, fluoro  
7 substituted alkyl of 1 to 6 carbons, OH, SH, alkoxy of 1 to 6 carbons, alkylthio  
8 of 1 to 6 carbons or benzyl;  
9  $m$  is an integer having the values 0 to 2;  
10  $R_4$  is independently H, alkyl of 1 to 6 carbons, or F; fluorosubstituted  
11 alkyl of 1 to 6 carbons, or halogen;  
12  $o$  is an integer having the values of 0 to 4;  
13  $n$  is an integer having the values of 0 to 4, and  
14  $R_8$  is H, alkyl of 1 to 6 carbons,  $-\text{CH}_2\text{O}(\text{C}_{1-6}\text{-alkyl})$ , or a cation of a  
15 pharmaceutically acceptable base.  
16 17. A method in accordance with Claim 16 wherein the compound has  
17 the formula



- 18 where  $R_2$  is H or halogen;  
19  $n$  is 0 or 1 and  
20  $R_8$  is H, alkyl of 1 to 6 carbons, or a cation of a pharmaceutically  
21 acceptable base.  
22 18. A method in accordance with Claim 17 wherein the compound is

1 [4-(2-cyclopropyl-4,4-dimethyl-1,2,3,4-tetrahydro-isoquinolin-6-yl-ethynyl)-  
2 2-fluoro-phenyl]-acetic acid or a salt with a pharmaceutically acceptable  
3 base.

4 19. A method in accordance with Claim 17 wherein the compound is  
5 [4-(2-cyclopropyl-4,4-dimethyl-1,2,3,4-tetrahydro-isoquinolin-6-yl-ethynyl)-  
6 phenyl]-acetic acid or a salt with a pharmaceutically acceptable base.

7 20. A method of inhibiting the enzyme cytochrome P450RAI in a  
8 mammal by administering to said mammal an effective dose of a  
9 pharmaceutical composition comprising a compound of the formula

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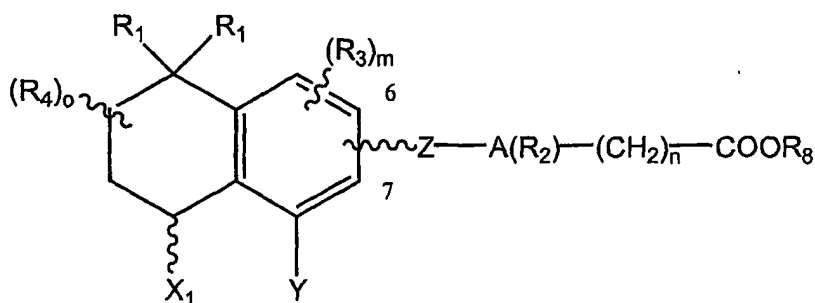
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17 wherein A is a phenyl or naphthyl group, or heteroaryl selected from a  
18 group consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl,  
19 thiazolyl, oxazolyl, imidazolyl and pyrazolyl, said phenyl and heteroaryl  
20 groups being optionally substituted with one or two  $R_2$  groups;

21  $X_1$  is 1-imidazolyl, or lower alkyl or halogen substituted 1-imidazolyl,  
22 OR, SR,  $NRR_6$  where R is H, alkyl of 1 to 6 carbons or benzyl;

23 Y is H, alkyl of 1 to 10 carbons, benzyl, lower alkyl or halogen  
24 substituted benzyl, fluoro-substituted alkyl of 1 to 10 carbons, cycloalkyl of 3  
25 to 6 carbons, lower alkyl substituted cycloalkyl of 3 to 6 carbons, Cl, Br, or I;

26 Z is  $-C\equiv C-$ ,

27  $-(CR_1=CR_1)_{n'}$ , where  $n'$  is an integer having the value 1 - 5,

28  $-CO-NR_1-$ ,

1 NR<sub>1</sub>-CO-,

2 -CO-O-,

3 -O-CO-,

4 -CS-NR<sub>1</sub>-,

5 NR<sub>1</sub>-CS-,

6 -CO-S-,

7 -S-CO-,

8 -N=N-;

9 R<sub>1</sub> is independently H or alkyl of 1 to 6 carbons;

10 R<sub>2</sub> is independently H, alkyl of 1 to 6 carbons, F, Cl, Br, I, fluoro  
11 substituted alkyl of 1 to 6 carbons, alkoxy of 1 to 6 carbons, or alkylthio of 1  
12 to 6 carbons;

13 R<sub>3</sub> is independently alkyl of 1 to 6 carbons, F, Cl, Br, I, fluoro  
14 substituted alkyl of 1 to 6 carbons, OH, SH, alkoxy of 1 to 6 carbons, alkylthio  
15 of 1 to 6 carbons or benzyl;

16 m is an integer having the values 0 to 2;

17 R<sub>4</sub> is independently H, alkyl of 1 to 6 carbons, or F; fluorosubstituted  
18 alkyl of 1 to 6 carbons, or halogen;

19 o is an integer having the values of 0 to 4;

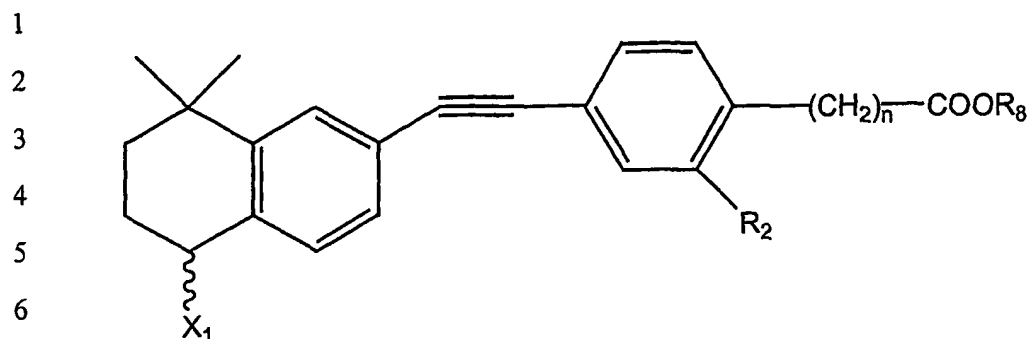
20 R<sub>6</sub> is H, lower alkyl, cycloalkyl of 3 to 6 carbons, lower alkyl  
21 substituted cycloalkyl of 3 to 6 carbons;

22 n is an integer having the values of 0 to 4, and

23 R<sub>8</sub> is H, alkyl of 1 to 6 carbons, -CH<sub>2</sub>O(C<sub>1-6</sub>-alkyl), or a cation of a  
24 pharmaceutically acceptable base, with the proviso that when Y is H, A is  
25 phenyl and X<sub>1</sub> is OH then n is 1 to 4.

26 21. A method in accordance with Claim 20 wherein the compound has  
27 the formula

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wherein  $X_1$  is 1-imidazolyl, or dialkyl-N or alkyl, cyclopropyl-N where the alkyl group has 1 to 6 carbons;

$R_2$  is H or halogen;

$n$  is 0 or 1, and

$R_8$  is H, alkyl of 1 to 6 carbons, or a cation of a pharmaceutically acceptable base.

**22.** A method in accordance with Claim 21 where the compound is selected from the group consisting of 4-[(5-cyclopropyl-methyl-amino)-8,8-dimethyl-5,6,7,8-tetrahydro-naphthalene-2-yl-ethynyl]-benzoic acid and 4-[5-(cyclopropyl-methyl-amino)-8,8-dimethyl-5,6,7,8-tetrahydro-naphthalene-2-yl-ethynyl]-2-fluoro benzoic acid or a salt with a pharmaceutically acceptable base or a  $C_{1-6}$  alkyl ester of said compound.

**23.** A method in accordance with Claim 21 where the compound is selected from the group consisting of 4-[(5-(cyclopropyl-methyl-amino)-8,8-dimethyl-5,6,7,8-tetrahydro-naphthalene-2-yl-ethynyl)-phenyl]-acetic acid and [4-(5-(cyclopropyl-methyl-amino)-8,8-dimethyl-5,6,7,8-tetrahydro-naphthalene-2-yl-ethynyl)-2-fluoro-phenyl]-acetic acid or a salt with a pharmaceutically acceptable base or a  $C_{1-6}$  alkyl ester of said compound.

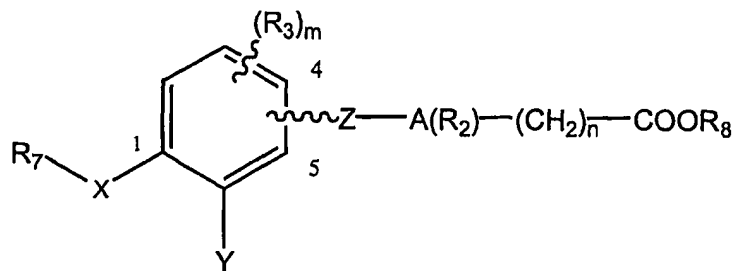
**24.** A method in accordance with Claim 21 where the compound is 4-[5-(*iso*-propyl-methyl-amino)-8,8-dimethyl-5,6,7,8-tetrahydro-naphthalene-2-yl-ethynyl]-benzoic acid or a salt with a pharmaceutically acceptable base or

1 a C<sub>1-6</sub> alkyl ester of said compound.

2 25. A method in accordance with Claim 21 where the compound is [4-  
3 (5-imidazol-1-yl-8,8-dimethyl-5,6,7,8-tetrahydro-naphthalen-2-yl-ethynyl)-  
4 benzoic acid or a salt with a pharmaceutically acceptable base or a C<sub>1-6</sub> alkyl  
5 ester of said compound.

6 26. A method in accordance with Claim 21 where the compound is [4-  
7 (5-imidazol-1-yl-8,8-dimethyl-5,6,7,8-tetrahydro-naphthalen-2-yl-ethynyl)-  
8 phenyl]-acetic acid or a salt with a pharmaceutically acceptable base or a C<sub>1-6</sub>  
9 alkyl ester of said compound.

10 27. A method of inhibiting the enzyme cytochrome P450RAI in a  
11 mammal by administering to said mammal an effective dose of a  
12 pharmaceutical composition comprising a compound of the formula  
13  
14  
15



21 wherein A is a phenyl or naphthyl group, or heteroaryl selected from a group  
22 consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl,  
23 thiazolyl, oxazolyl, imidazolyl and pyrazolyl, said phenyl and heteroaryl  
24 groups being optionally substituted with one or two R<sub>2</sub> groups;

25 X is O, S or NR where R is H, alkyl of 1 to 6 carbons, C<sub>1-6</sub>-trialkylsilyl  
26 or benzyl;

27 Y is H, alkyl of 1 to 10 carbons, benzyl, lower alkyl or halogen  
28 substituted benzyl, fluoro-substituted alkyl of 1 to 10 carbons, cycloalkyl of 3

1 to 6 carbons, lower alkyl substituted cycloalkyl of 3 to 6 carbons, Cl, Br, or I;

2 **Z** is  $-\text{C}\equiv\text{C}-$ ,

3  $-(\text{CR}_1=\text{CR}_1)_{n'}$ , where  $n'$  is an integer having the value 1 - 5,

4  $-\text{CO}-\text{NR}_1-$ ,

5  $\text{NR}_1-\text{CO}-$ ,

6  $-\text{CO}-\text{O}-$ ,

7  $-\text{O}-\text{CO}-$ ,

8  $-\text{CS}-\text{NR}_1-$ ,

9  $\text{NR}_1-\text{CS}-$ ,

10  $-\text{CO}-\text{S}-$ ,

11  $-\text{S}-\text{CO}-$ ,

12  $-\text{N}=\text{N}-$ ;

13 **R<sub>1</sub>** is independently H or alkyl of 1 to 6 carbons;

14 **R<sub>2</sub>** is independently H, alkyl of 1 to 6 carbons, F, Cl, Br, I, fluoro

15 substituted alkyl of 1 to 6 carbons, alkoxy of 1 to 6 carbons, or alkylthio of 1  
16 to 6 carbons;

17 **R<sub>3</sub>** is independently alkyl of 1 to 6 carbons, F, Cl, Br, I, fluoro

18 substituted alkyl of 1 to 6 carbons, OH, SH, alkoxy of 1 to 6 carbons, alkylthio  
19 of 1 to 6 carbons or benzyl;

20 **m** is an integer having the values 0 to 3;

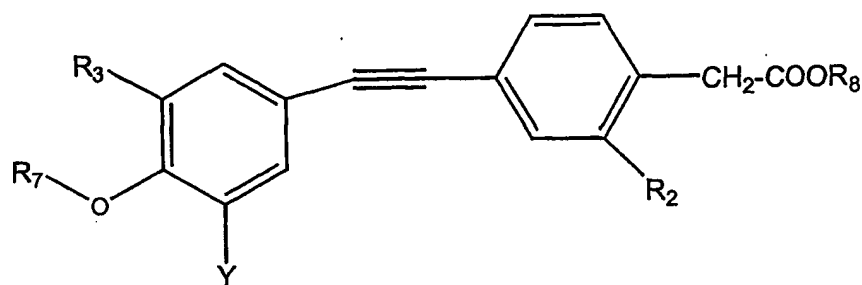
21 **R<sub>7</sub>** is H, alkyl of 1 to 6 carbons, cycloalkyl of 3 to 6 carbons or lower  
22 alkyl substituted cycloalkyl of 1 to 6 carbons;

23 **n** is an integer having the values of 1 to 4, and

24 **R<sub>8</sub>** is H, alkyl of 1 to 6 carbons,  $-\text{CH}_2\text{O}(\text{C}_{1-6}\text{-alkyl})$ , or a cation of a  
25 pharmaceutically acceptable base.

26 **28.** A method in accordance with Claim 27 wherein the compound has  
27 the formula

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wherein Y is branched-chain alkyl of 3 to 6 carbons;

R<sub>2</sub> is H or F;

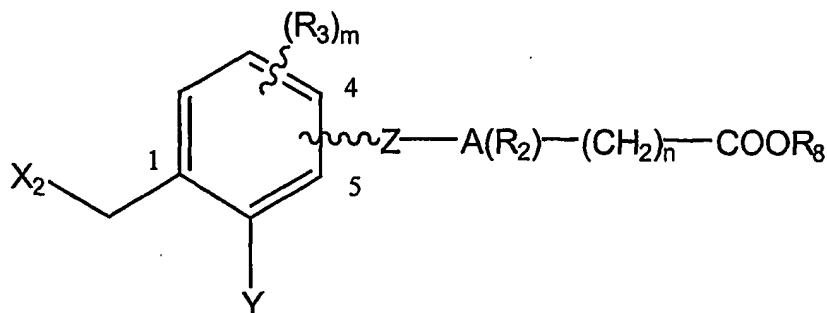
R<sub>3</sub> is branched-chain alkyl of 3 to 6 carbons;

R<sub>7</sub> is lower alkyl of 1 to 6 carbons, and

R<sub>8</sub> is H, alkyl of 1 to 6 carbons, -CH<sub>2</sub>O(C<sub>1-6</sub>-alkyl), or a cation of a pharmaceutically acceptable base.

29. A method in accordance with Claim 27 where the compound is selected from the group consisting of [4-(3,5-di-*tert*-butyl-4-methoxy-phenylethynyl)-phenyl]-acetic acid and [4-(3,5-di-*tert*-butyl-4-methoxy-phenylethynyl)-2-fluoro-phenyl]-acetic acid or a salt of said compound with a pharmaceutically acceptable base.

30. A method of inhibiting the enzyme cytochrome P450RAI in a mammal by administering to said mammal an effective dose of a pharmaceutical composition comprising a compound of the formula



wherein A is a phenyl or naphthyl group, or heteroaryl selected from a



1 group consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl,  
2 thiazolyl, oxazolyl, imidazolyl and pyrazolyl, said phenyl and heteroaryl  
3 groups being optionally substituted with one or two  $R_2$  groups;

4  $X_2$  is 1-imidazolyl, lower alkyl or halogen substituted 1-imidazolyl,  
5  $OR_7$ ,  $SR_7$  or  $NRR_7$  where  $R$  is H, alkyl of 1 to 6 carbons or benzyl;

6  $Y$  is H, alkyl of 1 to 10 carbons, benzyl, lower alkyl or halogen  
7 substituted benzyl, fluoro-substituted alkyl of 1 to 10 carbons, cycloalkyl of 3  
8 to 6 carbons, lower alkyl substituted cycloalkyl of 3 to 6 carbons, Cl, Br, or I;

9  $Z$  is  $-C\equiv C-$ ,

10  $-(CR_1=CR_1)_n$ , where  $n$  is an integer having the value 1 - 5,

11  $-CO-NR_1-$ ,

12  $NR_1-CO-$ ,

13  $-CO-O-$ ,

14  $-O-CO-$ ,

15  $-CS-NR_1-$ ,

16  $NR_1-CS-$ ,

17  $-CO-S-$ ,

18  $-S-CO-$ ,

19  $-N=N-$ ;

20  $R_1$  is independently H or alkyl of 1 to 6 carbons;

21  $R_2$  is independently H, alkyl of 1 to 6 carbons, F, Cl, Br, I, fluoro  
22 substituted alkyl of 1 to 6 carbons, alkoxy of 1 to 6 carbons, or alkylthio of 1  
23 to 6 carbons;

24  $R_3$  is alkyl of 1 to 6 carbons, F, Cl, Br, I, fluoro substituted alkyl of 1 to  
25 6 carbons, OH, SH, alkoxy of 1 to 6 carbons, alkylthio of 1 to 6 carbons or  
26 benzyl;

27  $m$  is an integer having the values 0 to 3;

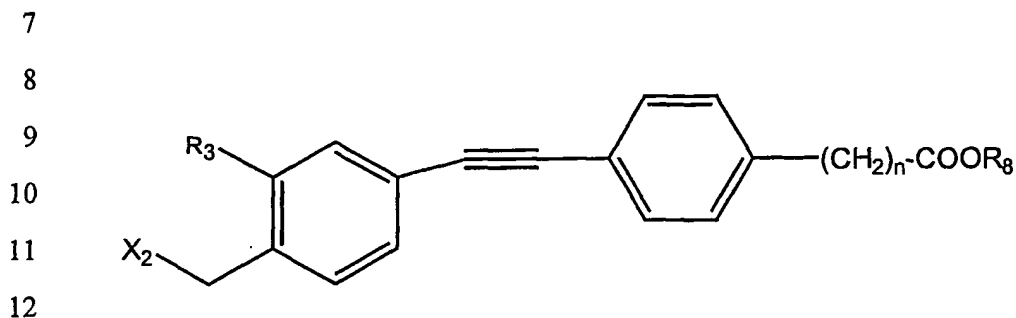
28  $R_7$  is H, alkyl of 1 to 6 carbons, cycloalkyl of 3 to 6 carbons, lower

1 alkyl substituted cycloalkyl of 3 to 6 carbons or C<sub>1-6</sub>-trialkylsilyl.

2 n is an integer having the values of 0 to 4, and

3 R<sub>8</sub> is H, alkyl of 1 to 6 carbons, -CH<sub>2</sub>O(C<sub>1-6</sub>-alkyl), or a cation of a  
4 pharmaceutically acceptable base.

5 31. A method in accordance with Claim 30 where the compound has  
6 the formula



13 wherein R<sub>3</sub> is alkyl of 1 to 6 carbons;

14 X<sub>2</sub> is 1-imidazolyl, OR<sub>7</sub>, or NRR<sub>7</sub> where R is alkyl of 1 to 6 carbons  
15 or cyclopropyl, and R<sub>7</sub> is alkyl of 1 to 6 carbons, cyclopropyl or lower alkyl  
16 substituted cyclopropyl;

17 n is 0 or 1, and

18 R<sub>8</sub> is H, alkyl of 1 to 6 carbons, or a cation of a pharmaceutically  
19 acceptable base.

20 32. A method in accordance with Claim 31 wherein the compound is  
21 selected from the group consisting of 4-(4-imidazol-1-yl-methyl-3-methyl-  
22 phenylethynyl)-benzoic acid and [4-(4-imidazol-1-yl-methyl-3-isopropyl-  
23 phenylethynyl)-phenyl]-benzoic acid or a salt of said compound with a  
24 pharmaceutically acceptable base or a C<sub>1-6</sub> alkyl ester of said compound.

25 33. A method in accordance with Claim 31 where the compound is  
26 selected from the group consisting of [4-(4-imidazol-1-yl-methyl-3-methyl-  
27 phenylethynyl)-phenyl]-acetic acid and [4-(4-imidazol-1-yl-methyl-3-  
28 isopropyl-phenylethynyl)-phenyl]-acetic acid or a salt of said compound with

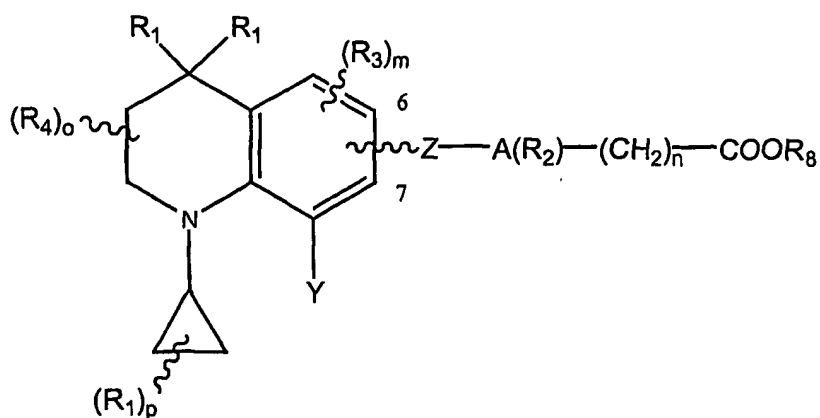
1 a pharmaceutically acceptable base or a C<sub>1-6</sub> alkyl ester of said compound.

2 34. A method in accordance with Claim 31 where the compound is  
3 selected from the group consisting of 4-{4-[(cyclopropyl-ethyl-amino)-  
4 methyl]-3-methyl-phenylethynyl}-benzoic and 4-{4-[(cyclopropyl-ethyl-  
5 amino)-methyl]-3-isopropyl-phenylethynyl}-benzoic acid or a salt of said  
6 compound with a pharmaceutically acceptable base or a C<sub>1-6</sub> alkyl ester of said  
7 compound.

8 35. A method in accordance with Claim 31 where the compound is (4-  
9 {4-[(cyclopropyl-ethyl-amino)-methyl]-3-methyl-phenylethynyl}-phenyl)-  
10 acetic acid or a salt of said compound with a pharmaceutically acceptable  
11 base or a C<sub>1-6</sub> alkyl ester of said compound.

12 36. A method in accordance with Claim 31 where the compound is {4-  
13 [3-isopropyl-4-(1-methyl-cyclopropoxymethyl)-phenylethynyl]-phenyl}-acetic  
14 acid or a salt of said compound with a pharmaceutically acceptable base or a  
15 C<sub>1-6</sub> alkyl ester of said compound.

16 37. A method of inhibiting the enzyme cytochrome P450RAI in a  
17 mammal by administering to said mammal as effective dose of a  
18 pharmaceutical composition comprising a compound of the formula



1 wherein A is a phenyl or naphthyl group, or heteroaryl selected from a  
2 group consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl,  
3 thiazolyl, oxazolyl, imidazolyl and pyrazolyl, said phenyl and heteroaryl  
4 groups being optionally substituted with one or two  $R_2$  groups;

5 Y is H, alkyl of 1 to 10 carbons, benzyl, lower alkyl or halogen  
6 substituted benzyl, fluoro-substituted alkyl of 1 to 10 carbons, cycloalkyl of 3  
7 to 6 carbons, lower alkyl substituted cycloalkyl of 3 to 6 carbons, F, Cl, Br, or  
8 I;

9 Z is -C≡C-,  
10  $-(CR_1=CR_1)_n$ , where n' is an integer having the value 1 - 5,  
11 -CO-NR<sub>1</sub>-,  
12 NR<sub>1</sub>-CO-,  
13 -CO-O-,  
14 -O-CO-,  
15 -CS-NR<sub>1</sub>-,  
16 NR<sub>1</sub>-CS-,  
17 -CO-S-,  
18 -S-CO-,  
19 -N=N-;

20  $R_1$  is independently H or alkyl of 1 to 6 carbons;

21 p is an integer having the values of 0 to 5;

22  $R_2$  is independently H, alkyl of 1 to 6 carbons, F, Cl, Br, I, CF<sub>3</sub>, fluoro  
23 substituted alkyl of 1 to 6 carbons, alkoxy of 1 to 6 carbons, or alkylthio of 1  
24 to 6 carbons;

25  $R_3$  is independently alkyl of 1 to 6 carbons, F, Cl, Br, I, CF<sub>3</sub>, fluoro  
26 substituted alkyl of 1 to 6 carbons, OH, SH, alkoxy of 1 to 6 carbons, alkylthio  
27 of 1 to 6 carbons or benzyl;

28 m is an integer having the values 0 to 2;

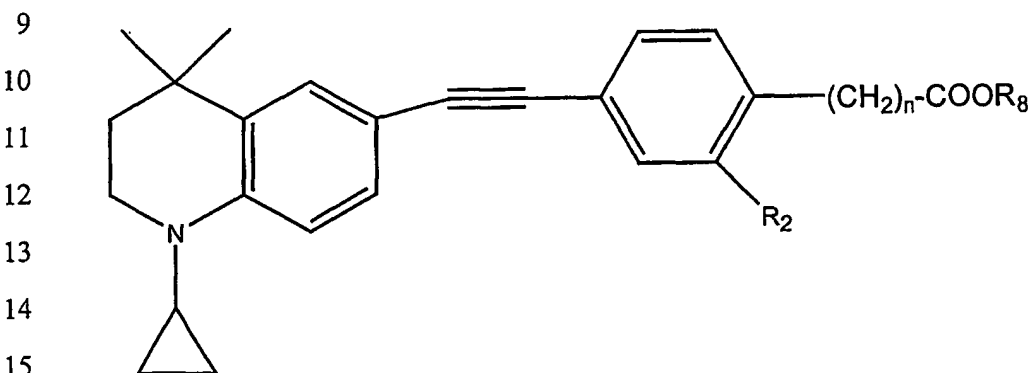
1  $R_4$  is independently H, alkyl of 1 to 6 carbons, or F; fluorosubstituted  
2 alkyl of 1 to 6 carbons, or halogen;

3  $o$  is an integer having the values of 0 to 4;

4  $n$  is an integer having the values of 0 to 4, and

5  $R_8$  is H, alkyl of 1 to 6 carbons,  $-\text{CH}_2\text{O}(\text{C}_{1-6}\text{-alkyl})$ , or a cation of a  
6 pharmaceutically acceptable base.

7 38. A method in accordance with Claim 37 where the compound has  
8 the formula



16 wherein  $R_2$  is hydrogen, alkyl of 1 to 6 carbons, or halogen

17  $n$  is 0 or 1, and

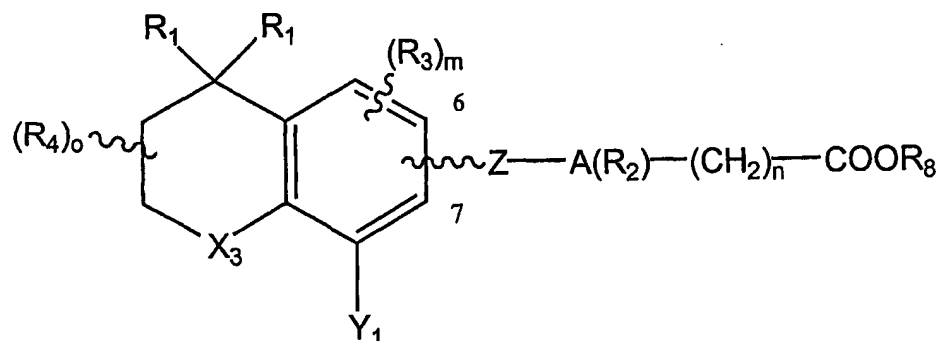
18  $R_8$  is H, alkyl of 1 to 6 carbons, or a cation of a pharmaceutically  
19 acceptable base.

20 39. A method in accordance with Claim 38 where the compound is 4-  
21 (1-cyclopropyl-4,4-dimethyl-1,2,3,4-tetrahydroquinolin-6-yl-ethynyl)-benzoic  
22 acid or a salt of said compound with a pharmaceutically acceptable base or a  
23  $\text{C}_{1-6}$  alkyl ester of said compound.

24 40. A method in accordance with Claim 38 where the compound is  
25 [4-(1-cyclopropyl-4,4-dimethyl-1,2,3,4-tetrahydro-quinolin-6-yl-  
26 ethynyl)phenyl] acetic acid methyl ester.

27 41. A method of inhibiting the enzyme cytochrome P450RAI in a  
28 mammal by administering to said mammal an effective dose of a

1 pharmaceutical composition comprising a compound of the formula



9 wherein A is a phenyl or naphthyl group, or heteroaryl selected from a  
10 group consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl,  
11 thiazolyl, oxazolyl, imidazolyl and pyrazolyl, said phenyl and heteroaryl  
12 groups being optionally substituted with one or two R<sub>2</sub> groups;

13 X<sub>3</sub> is S, or O, C(R<sub>1</sub>)<sub>2</sub>, or CO;

14 Y<sub>1</sub> is H, lower alkyl of 1 to 3 carbons, cycloalkyl of 3 to 6 carbons,  
15 benzyl, lower alkyl substituted cycloalkyl of 3 to 6 carbons;

16 Z is -C≡C-,

17 -(CR<sub>1</sub>=CR<sub>1</sub>)<sub>n</sub>, where n' is an integer having the value 1 - 5,

18 -CO-NR<sub>1</sub>-,

19 NR<sub>1</sub>-CO-,

20 -CO-O-,

21 -O-CO-,

22 -CS-NR<sub>1</sub>-,

23 NR<sub>1</sub>-CS-,

24 -CO-S-,

25 -S-CO-,

26 -N=N-;

27 R<sub>1</sub> is independently H or alkyl of 1 to 6 carbons;

28 R<sub>2</sub> is independently H, alkyl of 1 to 6 carbons, F, Cl, Br, I, CF<sub>3</sub>, fluoro

1 substituted alkyl of 1 to 6 carbons, alkoxy of 1 to 6 carbons, or alkylthio of 1  
2 to 6 carbons;

3  $R_3$  is independently alkyl of 1 to 6 carbons, F, Cl, Br, I,  $CF_3$ , fluoro  
4 substituted alkyl of 1 to 6 carbons, OH, SH, alkoxy of 1 to 6 carbons, alkylthio  
5 of 1 to 6 carbons or benzyl;

6  $m$  is an integer having the values 0 to 2;

7  $R_4$  is independently H, alkyl of 1 to 6 carbons, or F; fluorosubstituted  
8 alkyl of 1 to 6 carbons, or halogen;

9  $o$  is an integer having the values of 0 to 4;

10  $n$  is an integer having the values of 0 to 4, and

11  $R_8$  is H, alkyl of 1 to 6 carbons,  $-CH_2O(C_{1-6}\text{-alkyl})$ , or a cation of a  
12 pharmaceutically acceptable base, the compound meeting at least one of the  
13 provisos selected from the group consisting of:

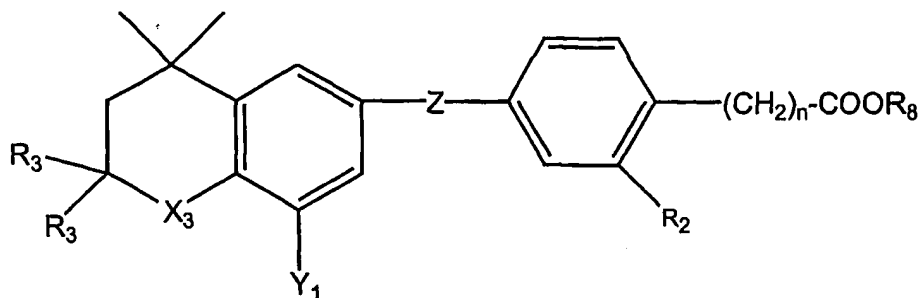
14  $Y_1$  is cycloalkyl,

15 when  $Y_1$  is not cycloalkyl then  $X_3$  is O or S and  $n$  is 1,

16 when  $Y_1$  is not cycloalkyl then  $X_3$  is CO, and  $n$  is 1,

17 when  $Y_1$  is not cycloalkyl then  $X_3$  is CO and the moiety A is  
18 substituted with at least one F group.

19 42. A method in accordance with Claim 41 where the compound has  
20 the formula



27 wherein  $R_2$  is H or F;

28  $R_3$  is H or lower alkyl of 1 to 6 carbons;

- 1           X<sub>3</sub> is O or CO;  
2           Y<sub>1</sub> is H, alkyl of 1 to 6 carbons, or cyclopropyl;  
3           Z is -C≡C- or -CO-O-;  
4           n is 0 or 1, and  
5           R<sub>8</sub> is H, alkyl of 1 to 6 carbons, or a cation of a pharmaceutically  
6 acceptable base, the compound meeting at least one of the provisos selected  
7 from the group consisting of:  
8           Y<sub>1</sub> is cyclopropyl,  
9           when Y<sub>1</sub> is not cyclopropyl then X<sub>3</sub> is O and n is 1,  
10           when Y<sub>1</sub> is not cyclopropyl then X<sub>3</sub> is CO, and n is 1,  
11           when Y<sub>1</sub> is not cyclopropyl then X<sub>3</sub> is CO and the moiety A is  
12 substituted with at least one F group.
- 13           43. A method in accordance with Claim 42 where the compound is 2-  
14 fluoro-4-(8,8-dimethyl-5-oxo-5,6,7,8-tetrahydro-naphthalen-2-yl-ethynyl)-  
15 benzoic acid or a salt of said compound with a pharmaceutically acceptable  
16 base or a C<sub>1-6</sub> alkyl ester of said compound.
- 17           44. A method in accordance with Claim 42 where the compound is  
18 selected from the group consisting of 4-[(8,8-dimethyl-5-oxo-5,6,7,8-  
19 tetrahydro-naphthalene-2-yl-ethynyl)-phenyl]-acetic acid and [2-fluoro-4-  
20 (8,8-dimethyl-5-oxo-5,6,7,8-tetrahydro-naphthalene-2-yl-ethynyl)phenyl]-  
21 acetic acid or a salt of said compound with a pharmaceutically acceptable  
22 base or a C<sub>1-6</sub> alkyl ester of said compound.
- 23           45. A method in accordance with Claim 42 where the compound is 2-  
24 fluoro-4-(2,2,4,4-tetramethyl-chroman-6-yl-ethynyl)-benzoic acid or a salt of  
25 said compound with a pharmaceutically acceptable base or a C<sub>1-6</sub> alkyl ester of  
26 said compound.
- 27           46. A method in accordance with Claim 42 where the compound is  
28 selected from the group consisting of [4-(2,2,4,4-tetramethyl-chroman-6-yl-



1 ethynyl) phenyl] acetic acid, [2-fluoro-4-(2,2,4,4-tetramethyl-chroman-6-yl-  
2 ethynyl) phenyl] acetic acid and [4-(8-ethyl-2,2,4,4-tetramethyl-chroman-6-yl-  
3 ethynyl) phenyl] acetic acid or a salt of said compound with a  
4 pharmaceutically acceptable base or a C<sub>1-6</sub> alkyl ester of said compound.

5       **47.** A method in accordance with Claim 42 where the compound is 4-  
6 (8-cyclopropyl-2,2,4,4-tetramethyl-chroman-6-yl-ethynyl)-benzoic acid or a  
7 salt of said compound with a pharmaceutically acceptable base or a C<sub>1-6</sub> alkyl  
8 ester of said compound.

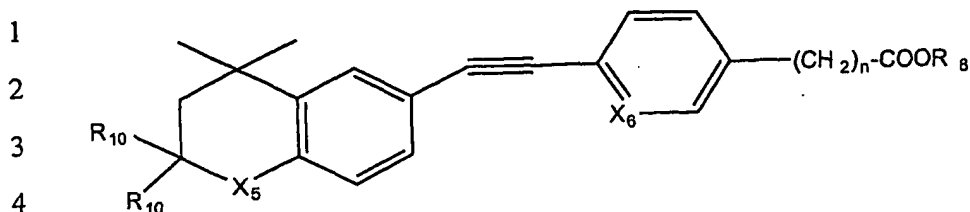
9       **48.** A method in accordance with Claim 42 where the compound is  
10 selected from the group consisting of [4-(8-cyclopropyl-2,2,4,4-tetramethyl-  
11 chroman-6-yl-ethynyl) phenyl] acetic acid and [4-(8-cyclopropyl-2,2,4,4-  
12 tetramethyl-chroman-6-yl-ethynyl)-2-fluorophenyl] acetic acid or a salt of  
13 said compound with a pharmaceutically acceptable base or a C<sub>1-6</sub> alkyl ester of  
14 said compound.

15       **49.** A method in accordance with Claim 42 where the compound is  
16 8,8-dimethyl-5-oxo-5,6,7,8-tetrahydro-naphthalene-2-carboxylic acid-4-  
17 (carboxymethyl)phenyl ester or a salt of said compound with a  
18 pharmaceutically acceptable base or a C<sub>1-6</sub> alkyl ester of said compound.

19       **50.** A method in accordance with Claim 42 where the compound is  
20 2,2,4,4-tetramethyl-chroman-6-carboxylic acid 4-(carboxymethyl)phenyl ester  
21 or a salt of said compound with a pharmaceutically acceptable base or a C<sub>1-6</sub>  
22 alkyl ester of said compound.

23       **51.** A method of inhibiting the enzyme cytochrome P450RAI in a  
24 mammal by administering to said mammal an effective dose of a  
25 pharmaceutical composition comprising a compound selected from the group  
26 of compounds wherein the variables for each compound are defined as  
27 follows with reference to the formula below:

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5  $X_5$  is O,  $X_6$  is CH,  $n$  is 0 and  $R_8$  is H, alkyl of 1 to 6 carbons, -  
6  $CH_2O(C_{1-6}\text{-alkyl})$ , or a cation of a pharmaceutically acceptable base;

7  $X_5$  is S,  $X_6$  is CH,  $n$  is 1 and  $R_8$  is H, alkyl of 1 to 6 carbons, -  
8  $CH_2O(C_{1-6}\text{-alkyl})$ , or a cation of a pharmaceutically acceptable base;

9  $X_5$  is S,  $X_6$  is CH,  $n$  is 2 and  $R_8$  is H, alkyl of 1 to 6 carbons, -  
10  $CH_2O(C_{1-6}\text{-alkyl})$ , or a cation of a pharmaceutically acceptable base;

11  $X_5$  is S,  $X_6$  is CH,  $n$  is 0 and  $R_8$  is H, alkyl of 1 to 6 carbons, -  
12  $CH_2O(C_{1-6}\text{-alkyl})$ , or a cation of a pharmaceutically acceptable base; and

13  $X_5$  is S,  $X_6$  is N,  $n$  is 0 and  $R_8$  is H, alkyl of 1 to 6 carbons,  $-CH_2O(C_{1-}$   
14  $6\text{-alkyl})$ , or a cation of a pharmaceutically acceptable base.

15 **52.** A method in accordance with Claim 51 wherein the compound is  
16 selected from the group of compounds wherein the variables for each  
17 compound are defined as follows:

18  $X_5$  is O,  $X_6$  is CH,  $n$  is 0 and  $R_8$  is H or a cation of a pharmaceutically  
19 acceptable base;

20  $X_5$  is S,  $X_6$  is CH,  $n$  is 1 and  $R_8$  is H or a cation of a pharmaceutically  
21 acceptable base;

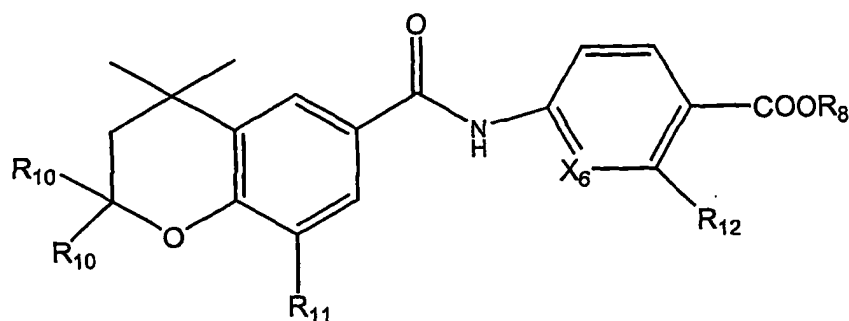
22  $X_5$  is S,  $X_6$  is CH,  $n$  is 2 and  $R_8$  is H or a cation of a pharmaceutically  
23 acceptable base;

24  $X_5$  is S,  $X_6$  is CH,  $n$  is 0 and  $R_8$  is H or a cation of a pharmaceutically  
25 acceptable base; and

26  $X_5$  is S,  $X_6$  is N,  $n$  is 0 and  $R_8$  is H or a cation of a pharmaceutically  
27 acceptable base.

28 **53.** A method of inhibiting the enzyme cytochrome P450RAI in a

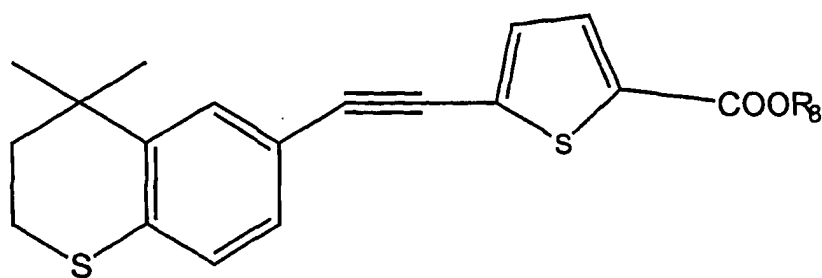
1 mammal by administering to said mammal an effective dose of a  
 2 pharmaceutical composition comprising a compound shown by the formula



10 wherein the variable  $R_8$  is H, alkyl of 1 to 6 carbons,  $-\text{CH}_2\text{O}(\text{C}_{1-6}$ -  
 11 alkyl), or a cation of a pharmaceutically acceptable base.

12 **54.** A method in accordance with Claim 53 wherein in the formula of  
 13 the compound  $R_8$  is H or a cation of a pharmaceutically acceptable base.

14 **55.** A method of inhibiting the enzyme cytochrome P450RAI in a  
 15 mammal by administering to said mammal an effective dose of a  
 16 pharmaceutical composition comprising a compound selected from the group  
 17 of compounds wherein the variables for each compound are defined as  
 18 follows with reference to the formula below:



25  $R_{10}$  is  $\text{CH}_3$ ,  $R_{11}$  is Cl,  $R_{12}$  is F,  $X_6$  is CH and  $R_8$  is H, alkyl of 1 to 6  
 26 carbons,  $-\text{CH}_2\text{O}(\text{C}_{1-6}$ -alkyl), or a cation of a pharmaceutically acceptable  
 27 base;

28  $R_{10}$  is  $\text{CH}_3$ ,  $R_{11}$  is cyclopropyl,  $R_{12}$  is F,  $X_6$  is CH and  $R_8$  is H, alkyl of

1 1 to 6 carbons,  $-\text{CH}_2\text{O}(\text{C}_{1-6}\text{-alkyl})$ , or a cation of a pharmaceutically  
2 acceptable base;

3  $\text{R}_{10}$  is  $\text{CH}_3$ ,  $\text{R}_{11}$  is  $\text{CF}_3$ ,  $\text{R}_{12}$  is F,  $\text{X}_6$  is CH and  $\text{R}_8$  is H, alkyl of 1 to 6  
4 carbons,  $-\text{CH}_2\text{O}(\text{C}_{1-6}\text{-alkyl})$ , or a cation of a pharmaceutically acceptable  
5 base;

6  $\text{R}_{10}$  is  $\text{CH}_3\text{CH}_2$ ,  $\text{R}_{11}$  is Br,  $\text{R}_{12}$  is F,  $\text{X}_6$  is CH and  $\text{R}_8$  is H, alkyl of 1  
7 to 6 carbons,  $-\text{CH}_2\text{O}(\text{C}_{1-6}\text{-alkyl})$ , or a cation of a pharmaceutically acceptable  
8 base;

9  $\text{R}_{10}$  is  $\text{CH}_3$ ,  $\text{R}_{11}$  is  $\text{CH}_3$ ,  $\text{R}_{12}$  is F,  $\text{X}_6$  is CH and  $\text{R}_8$  is H, alkyl of 1 to 6  
10 carbons,  $-\text{CH}_2\text{O}(\text{C}_{1-6}\text{-alkyl})$ , or a cation of a pharmaceutically acceptable  
11 base;

12  $\text{R}_{10}$  is  $\text{CH}_3$ ,  $\text{R}_{11}$  is Cl,  $\text{R}_{12}$  is F,  $\text{X}_6$  is N and  $\text{R}_8$  is H, alkyl of 1 to 6  
13 carbons,  $-\text{CH}_2\text{O}(\text{C}_{1-6}\text{-alkyl})$ , or a cation of a pharmaceutically acceptable  
14 base;

15  $\text{R}_{10}$  is  $\text{CH}_3$ ,  $\text{R}_{11}$  is phenyl,  $\text{R}_{12}$  is F,  $\text{X}_6$  is CH and  $\text{R}_8$  is H, alkyl of 1 to  
16 6 carbons,  $-\text{CH}_2\text{O}(\text{C}_{1-6}\text{-alkyl})$ , or a cation of a pharmaceutically acceptable  
17 base;

18  $\text{R}_{10}$  is H,  $\text{R}_{11}$  is Br,  $\text{R}_{12}$  is F,  $\text{X}_6$  is CH and  $\text{R}_8$  is H, alkyl of 1 to 6  
19 carbons,  $-\text{CH}_2\text{O}(\text{C}_{1-6}\text{-alkyl})$ , or a cation of a pharmaceutically acceptable  
20 base;

21  $\text{R}_{10}$  is  $\text{CH}_3$ ,  $\text{R}_{11}$  is  $\text{OCH}_3$ ,  $\text{R}_{12}$  is F,  $\text{X}_6$  is CH and  $\text{R}_8$  is H, alkyl of 1 to 6  
22 carbons,  $-\text{CH}_2\text{O}(\text{C}_{1-6}\text{-alkyl})$ , or a cation of a pharmaceutically acceptable  
23 base;

24  $\text{R}_{10}$  is  $\text{CH}_3$ ,  $\text{R}_{11}$  is  $\text{CH}_3$ ,  $\text{R}_{12}$  is H,  $\text{X}_6$  is CH and  $\text{R}_8$  is H, alkyl of 1 to 6  
25 carbons,  $-\text{CH}_2\text{O}(\text{C}_{1-6}\text{-alkyl})$ , or a cation of a pharmaceutically acceptable  
26 base;

27  $\text{R}_{10}$  is  $\text{CH}_3$ ,  $\text{R}_{11}$  is H,  $\text{R}_{12}$  is F,  $\text{X}_6$  is CH and  $\text{R}_8$  is H, alkyl of 1 to 6  
28 carbons,  $-\text{CH}_2\text{O}(\text{C}_{1-6}\text{-alkyl})$ , or a cation of a pharmaceutically acceptable

1 base;

2  $R_{10}$  is  $CH_3$ ,  $R_{11}$  is Br,  $R_{12}$  is F,  $X_6$  is CH and  $R_8$  is H, alkyl of 1 to 6  
3 carbons,  $-CH_2O(C_{1-6}\text{-alkyl})$ , or a cation of a pharmaceutically acceptable  
4 base;

5  $R_{10}$  is  $CH_3$ ,  $R_{11}$  is  $CF_3CF_2$ ,  $R_{12}$  is F,  $X_6$  is CH and  $R_8$  is H, alkyl of 1  
6 to 6 carbons,  $-CH_2O(C_{1-6}\text{-alkyl})$ , or a cation of a pharmaceutically acceptable  
7 base;

8  $R_{10}$  is  $CH_3$ ,  $R_{11}$  is  $CH_3CH_2$ ,  $R_{12}$  is F,  $X_6$  is CH and  $R_8$  is H, alkyl of 1  
9 to 6 carbons,  $-CH_2O(C_{1-6}\text{-alkyl})$ , or a cation of a pharmaceutically acceptable  
10 base;

11  $R_{10}$  is  $CH_3$ ,  $R_{11}$  is *iso*-propyl,  $R_{12}$  is F,  $X_6$  is CH and  $R_8$  is H, alkyl of 1  
12 to 6 carbons,  $-CH_2O(C_{1-6}\text{-alkyl})$ , or a cation of a pharmaceutically acceptable  
13 base;

14  $R_{10}$  is  $CH_3$ ,  $R_{11}$  is (1-methyl)cyclopropyl,  $R_{12}$  is F,  $X_6$  is CH and  $R_8$  is  
15 H, alkyl of 1 to 6 carbons,  $-CH_2O(C_{1-6}\text{-alkyl})$ , or a cation of a  
16 pharmaceutically acceptable base;

17  $R_{10}$  is  $CH_3$ ,  $R_{11}$  is *tertiary*-butyl,  $R_{12}$  is F,  $X_6$  is CH and  $R_8$  is H, alkyl  
18 of 1 to 6 carbons,  $-CH_2O(C_{1-6}\text{-alkyl})$ , or a cation of a pharmaceutically  
19 acceptable base;

20  $R_{10}$  is  $CH_3$ ,  $R_{11}$  is (2,2-difluoro)cyclopropyl,  $R_{12}$  is F,  $X_6$  is CH and  $R_8$   
21 is H, alkyl of 1 to 6 carbons,  $-CH_2O(C_{1-6}\text{-alkyl})$ , or a cation of a  
22 pharmaceutically acceptable base and

23  $R_{10}$  is  $CH_3$ ,  $R_{11}$  is (cyclopropyl)methyl,  $R_{12}$  is F,  $X_6$  is CH and  $R_8$  is H,  
24 alkyl of 1 to 6 carbons,  $-CH_2O(C_{1-6}\text{-alkyl})$ , or a cation of a pharmaceutically  
25 acceptable base.

26 **56.** A method in accordance with Claim 55 wherein the compound is  
27 selected from the group of compounds wherein the variables for each  
28 compound are defined as follows:

- 1         $R_{10}$  is  $CH_3$ ,  $R_{11}$  is  $Cl$ ,  $R_{12}$  is  $F$ ,  $X_6$  is  $CH$  and  $R_8$  is  $H$  or a cation of a  
2        pharmaceutically acceptable base;
- 3         $R_{10}$  is  $CH_3$ ,  $R_{11}$  is cyclopropyl,  $R_{12}$  is  $F$ ,  $X_6$  is  $CH$  and  $R_8$  is  $H$  or a  
4        cation of a pharmaceutically acceptable base;
- 5         $R_{10}$  is  $CH_3$ ,  $R_{11}$  is  $CF_3$ ,  $R_{12}$  is  $F$ ,  $X_6$  is  $CH$  and  $R_8$  is  $H$  or a cation of a  
6        pharmaceutically acceptable base;
- 7         $R_{10}$  is  $CH_3CH_2$ ,  $R_{11}$  is  $Br$ ,  $R_{12}$  is  $F$ ,  $X_6$  is  $CH$  and  $R_8$  is  $H$  or a cation  
8        of a pharmaceutically acceptable base;
- 9         $R_{10}$  is  $CH_3$ ,  $R_{11}$  is  $CH_3$ ,  $R_{12}$  is  $F$ ,  $X_6$  is  $CH$  and  $R_8$  is  $H$  or a cation of a  
10        pharmaceutically acceptable base;
- 11         $R_{10}$  is  $CH_3$ ,  $R_{11}$  is  $Cl$ ,  $R_{12}$  is  $F$ ,  $X_6$  is  $N$  and  $R_8$  is  $H$  or a cation of a  
12        pharmaceutically acceptable base;
- 13         $R_{10}$  is  $CH_3$ ,  $R_{11}$  is phenyl,  $R_{12}$  is  $F$ ,  $X_6$  is  $CH$  and  $R_8$  is  $H$  or a cation of  
14        a pharmaceutically acceptable base;
- 15         $R_{10}$  is  $H$ ,  $R_{11}$  is  $Br$ ,  $R_{12}$  is  $F$ ,  $X_6$  is  $CH$  and  $R_8$  is  $H$  or a cation of a  
16        pharmaceutically acceptable base;
- 17         $R_{10}$  is  $CH_3$ ,  $R_{11}$  is  $OCH_3$ ,  $R_{12}$  is  $F$ ,  $X_6$  is  $CH$  and  $R_8$  is  $H$  or a cation of  
18        a pharmaceutically acceptable base;
- 19         $R_{10}$  is  $CH_3$ ,  $R_{11}$  is  $CH_3$ ,  $R_{12}$  is  $H$ ,  $X_6$  is  $CH$  and  $R_8$  is  $H$  or a cation of a  
20        pharmaceutically acceptable base;
- 21         $R_{10}$  is  $CH_3$ ,  $R_{11}$  is  $H$ ,  $R_{12}$  is  $F$ ,  $X_6$  is  $CH$  and  $R_8$  is  $H$  or a cation of a  
22        pharmaceutically acceptable base;
- 23         $R_{10}$  is  $CH_3$ ,  $R_{11}$  is  $Br$ ,  $R_{12}$  is  $F$ ,  $X_6$  is  $CH$  and  $R_8$  is  $H$  or a cation of a  
24        pharmaceutically acceptable base;
- 25         $R_{10}$  is  $CH_3$ ,  $R_{11}$  is  $CF_3CF_2$ ,  $R_{12}$  is  $F$ ,  $X_6$  is  $CH$  and  $R_8$  is  $H$  or a cation  
26        of a pharmaceutically acceptable base;
- 27         $R_{10}$  is  $CH_3$ ,  $R_{11}$  is  $CH_3CH_2$ ,  $R_{12}$  is  $F$ ,  $X_6$  is  $CH$  and  $R_8$  is  $H$  or a cation  
28        of a pharmaceutically acceptable base;

1  $R_{10}$  is  $CH_3$ ,  $R_{11}$  is *iso*-propyl,  $R_{12}$  is F,  $X_6$  is CH and  $R_8$  is H or a cation  
2 of a pharmaceutically acceptable base;

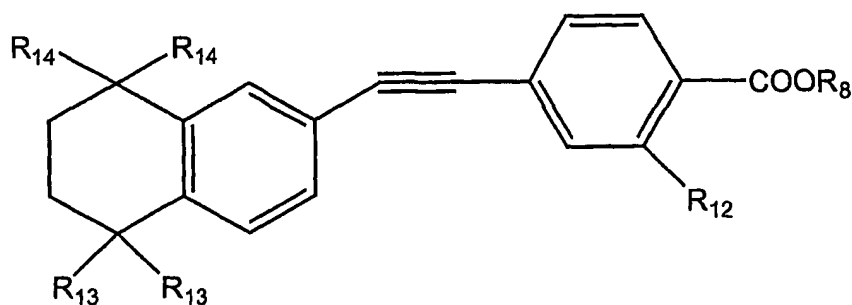
3  $R_{10}$  is  $CH_3$ ,  $R_{11}$  is (1-methyl)cyclopropyl,  $R_{12}$  is F,  $X_6$  is CH and  $R_8$  is  
4 H or a cation of a pharmaceutically acceptable base;

5  $R_{10}$  is  $CH_3$ ,  $R_{11}$  is *tertiary*-butyl,  $R_{12}$  is F,  $X_6$  is CH and  $R_8$  is H or a  
6 cation of a pharmaceutically acceptable base;

7  $R_{10}$  is  $CH_3$ ,  $R_{11}$  is (2,2-difluoro)cyclopropyl,  $R_{12}$  is F,  $X_6$  is CH and  $R_8$   
8 is H or a cation of a pharmaceutically acceptable base, and

9  $R_{10}$  is  $CH_3$ ,  $R_{11}$  is (cyclopropyl)methyl,  $R_{12}$  is F,  $X_6$  is CH and  $R_8$  is H  
10 or a cation of a pharmaceutically acceptable base.

11 57. A method of inhibiting the enzyme cytochrome P450RAI in a  
12 mammal by administering to said mammal an effective dose of a  
13 pharmaceutical composition comprising a compound selected from the group  
14 of compounds wherein the variables for each compound are defined as follows  
15 with reference to the formula below:



23  $R_{12}$  is H, the two  $R_{13}$  groups jointly represent an oxo ( $=O$ ) function and  
24  $R_{14}$  is  $CH_3$  and  $R_8$  is H, alkyl of 1 to 6 carbons,  $-CH_2O(C_{1-6}\text{-alkyl})$ , or a  
25 cation of a pharmaceutically acceptable base;

26  $R_{12}$  is H,  $R_{13}$  is H,  $R_{14}$  is  $CH_3$  and  $R_8$  is H, alkyl of 1 to 6 carbons, -  
27  $CH_2O(C_{1-6}\text{-alkyl})$ , or a cation of a pharmaceutically acceptable base;

28  $R_{12}$  is H,  $R_{13}$  is  $CH_3$ ,  $R_{14}$  is  $CH_3$  and  $R_8$  is H, alkyl of 1 to 6 carbons, -

- 1 CH<sub>2</sub>O(C<sub>1-6</sub>-alkyl), or a cation of a pharmaceutically acceptable base;  
2 R<sub>12</sub> is H, R<sub>13</sub> is CH<sub>3</sub>, R<sub>14</sub> is H and R<sub>8</sub> is H, alkyl of 1 to 6 carbons, -  
3 CH<sub>2</sub>O(C<sub>1-6</sub>-alkyl), or a cation of a pharmaceutically acceptable base;  
4 R<sub>12</sub> is F, R<sub>13</sub> is CH<sub>3</sub>, R<sub>14</sub> is CH<sub>3</sub> and R<sub>8</sub> is H, alkyl of 1 to 6 carbons, -  
5 CH<sub>2</sub>O(C<sub>1-6</sub>-alkyl), or a cation of a pharmaceutically acceptable base, and  
6 R<sub>12</sub> is H, one of the R<sub>13</sub> groups is H, the other is OH, R<sub>14</sub> is CH<sub>3</sub> and  
7 R<sub>8</sub> is H, alkyl of 1 to 6 carbons, -CH<sub>2</sub>O(C<sub>1-6</sub>-alkyl), or a cation of a  
8 pharmaceutically acceptable base.

9 58. A method in accordance with Claim 57 wherein the compound is  
10 selected from the group of compounds wherein the variables for each  
11 compound are defined as follows:

- 12 R<sub>12</sub> is H, the two R<sub>13</sub> groups jointly represent an oxo (=O) function and  
13 R<sub>14</sub> is CH<sub>3</sub> and R<sub>8</sub> is H or a cation of a pharmaceutically acceptable base;

- 14 R<sub>12</sub> is H, R<sub>13</sub> is H, R<sub>14</sub> is CH<sub>3</sub> and R<sub>8</sub> is H or a cation of a  
15 pharmaceutically acceptable base;

- 16 R<sub>12</sub> is H, R<sub>13</sub> is CH<sub>3</sub>, R<sub>14</sub> is CH<sub>3</sub> and R<sub>8</sub> is H or a cation of a  
17 pharmaceutically acceptable base;

- 18 R<sub>12</sub> is H, R<sub>13</sub> is CH<sub>3</sub>, R<sub>14</sub> is H and R<sub>8</sub> is H or a cation of a  
19 pharmaceutically acceptable base;

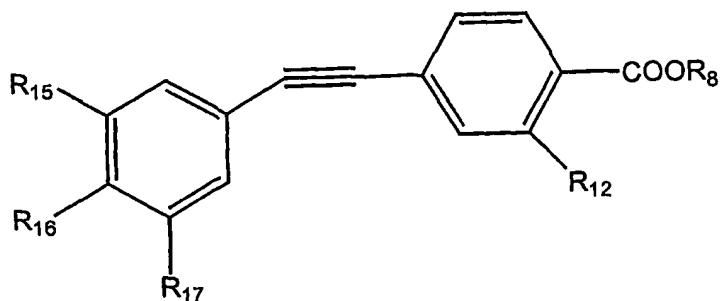
- 20 R<sub>12</sub> is F, R<sub>13</sub> is CH<sub>3</sub>, R<sub>14</sub> is CH<sub>3</sub> and R<sub>8</sub> is H or a cation of a  
21 pharmaceutically acceptable base, and

- 22 R<sub>12</sub> is H, one of the R<sub>13</sub> groups is H, the other is OH, R<sub>14</sub> is CH<sub>3</sub> and  
23 R<sub>8</sub> is H or a cation of a pharmaceutically acceptable base.

24 59. A method of inhibiting the enzyme cytochrome P450RAI in a  
25 mammal by administering to said mammal an effective dose of a  
26 pharmaceutical composition comprising a compound selected from the group  
27 of compounds wherein the variables for each compound are defined as  
28 follows with reference to the formula below:



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**R<sub>12</sub>** is H, **R<sub>15</sub>** is *tertiary*-butyl, **R<sub>16</sub>** is OH, **R<sub>17</sub>** is Cl and **R<sub>8</sub>** is H, alkyl of 1 to 6 carbons, -CH<sub>2</sub>O(C<sub>1-6</sub>-alkyl), or a cation of a pharmaceutically acceptable base;

**R<sub>12</sub>** is H, **R<sub>15</sub>** is *tertiary*-butyl, **R<sub>16</sub>** is OCH<sub>3</sub>, **R<sub>17</sub>** is *tertiary*-butyl and **R<sub>8</sub>** is H, alkyl of 1 to 6 carbons, -CH<sub>2</sub>O(C<sub>1-6</sub>-alkyl), or a cation of a pharmaceutically acceptable base;

**R<sub>12</sub>** is H, **R<sub>15</sub>** is 1-adamantyl, **R<sub>16</sub>** is OCH<sub>3</sub>, **R<sub>17</sub>** is H and **R<sub>8</sub>** is H, alkyl of 1 to 6 carbons, -CH<sub>2</sub>O(C<sub>1-6</sub>-alkyl), or a cation of a pharmaceutically acceptable base;

**R<sub>12</sub>** is H, **R<sub>15</sub>** is *tertiary*-butyl, **R<sub>16</sub>** is OH, **R<sub>17</sub>** is *tertiary*-butyl and **R<sub>8</sub>** is H, alkyl of 1 to 6 carbons, -CH<sub>2</sub>O(C<sub>1-6</sub>-alkyl), or a cation of a pharmaceutically acceptable base, and

**R<sub>12</sub>** is F, **R<sub>15</sub>** is *tertiary*-butyl, **R<sub>16</sub>** is OH, **R<sub>17</sub>** is H and **R<sub>8</sub>** is H, alkyl of 1 to 6 carbons, -CH<sub>2</sub>O(C<sub>1-6</sub>-alkyl), or a cation of a pharmaceutically acceptable base.

**60.** A method in accordance with Claim 59 wherein the compound is selected from the group of compounds wherein the variables for each compound are defined as follows:

**R<sub>12</sub>** is H, **R<sub>15</sub>** is *tertiary*-butyl, **R<sub>16</sub>** is OH, **R<sub>17</sub>** is Cl and **R<sub>8</sub>** is H or a cation of a pharmaceutically acceptable base;

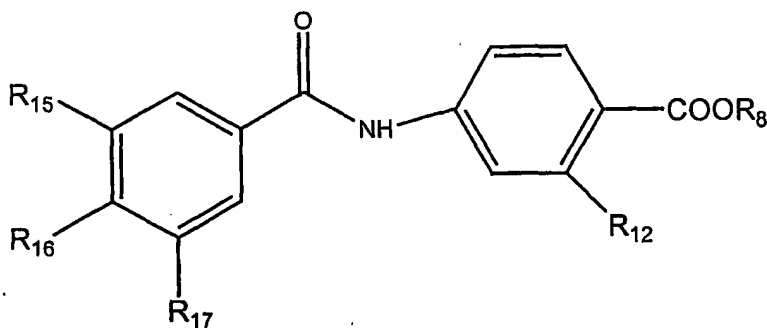
**R<sub>12</sub>** is H, **R<sub>15</sub>** is *tertiary*-butyl, **R<sub>16</sub>** is OCH<sub>3</sub>, **R<sub>17</sub>** is *tertiary*-butyl and **R<sub>8</sub>** is H or a cation of a pharmaceutically acceptable base;

1  $R_{12}$  is H,  $R_{15}$  is 1-adamantyl,  $R_{16}$  is  $OCH_3$ ,  $R_{17}$  is H and  $R_8$  is H or a  
 2 cation of a pharmaceutically acceptable base;

3  $R_{12}$  is H,  $R_{15}$  is *tertiary*-butyl,  $R_{16}$  is OH,  $R_{17}$  is *tertiary*-butyl and  $R_8$   
 4 is H or a cation of a pharmaceutically acceptable base, and

5  $R_{12}$  is F,  $R_{15}$  is *tertiary*-butyl,  $R_{16}$  is OH,  $R_{17}$  is H and  $R_8$  is H or a  
 6 cation of a pharmaceutically acceptable base.

7 61. A method of inhibiting the enzyme cytochrome P450RAI in a  
 8 mammal by administering to said mammal an effective dose of a  
 9 pharmaceutical composition comprising a compound selected from the group  
 10 of compounds wherein the variables for each compound are defined as  
 11 follows with reference to the formula below:



19  $R_{12}$  is F,  $R_{15}$  is *tertiary*-butyl,  $R_{16}$  is  $CH_3CH_2O$ ,  $R_{17}$  is I and  $R_8$  is H,  
 20 alkyl of 1 to 6 carbons,  $-CH_2O(C_{1-6}\text{-alkyl})$ , or a cation of a pharmaceutically  
 21 acceptable base, and

22  $R_{12}$  is F,  $R_{15}$  is *tertiary*-butyl,  $R_{16}$  is  $CH_3CH_2O$ ,  $R_{17}$  is Br and  $R_8$  is H,  
 23 alkyl of 1 to 6 carbons,  $-CH_2O(C_{1-6}\text{-alkyl})$ , or a cation of a pharmaceutically  
 24 acceptable base.

25 62. A method in accordance with Claim 61 wherein the compound is  
 26 selected from the group of compounds wherein the variables for each  
 27 compound are defined as follows:

28  $R_{12}$  is F,  $R_{15}$  is *tertiary*-butyl,  $R_{16}$  is  $CH_3CH_2O$ ,  $R_{17}$  is I and  $R_8$  is H or

1 a cation of a pharmaceutically acceptable base, and

2  $R_{12}$  is F,  $R_{15}$  is *tertiary*-butyl,  $R_{16}$  is  $CH_3CH_2O$ ,  $R_{17}$  is Br and  $R_8$  is H

3 or a cation of a pharmaceutically acceptable base.

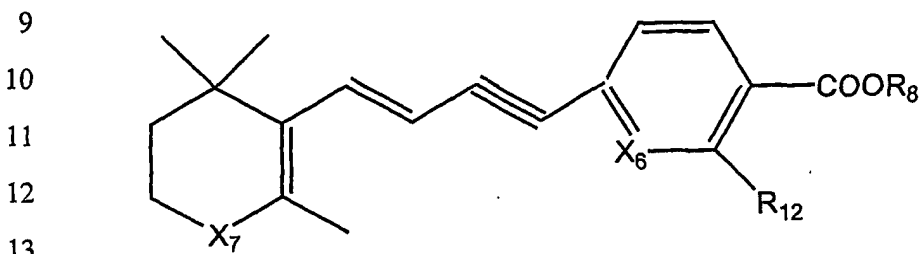
4 63. A method of inhibiting the enzyme cytochrome P450RAI in a

5 mammal by administering to said mammal an effective dose of a

6 pharmaceutical composition comprising a compound selected from the group

7 of compounds wherein the variables for each compound are defined as

8 follows with reference to the formula below:



14  $R_{12}$  is H,  $X_6$  is CH,  $X_7$  is  $(CH_3)_2C$  and  $R_8$  is H, alkyl of 1 to 6 carbons,  
15  $-CH_2O(C_{1-6}\text{-alkyl})$ , or a cation of a pharmaceutically acceptable base;

16  $R_{12}$  is H,  $X_6$  is CH,  $X_7$  is  $CH_2$  and  $R_8$  is H, alkyl of 1 to 6 carbons, -  
17  $CH_2O(C_{1-6}\text{-alkyl})$ , or a cation of a pharmaceutically acceptable base;

18  $R_{12}$  is H,  $X_6$  is CH,  $X_7$  is S and  $R_8$  is H, alkyl of 1 to 6 carbons, -  
19  $CH_2O(C_{1-6}\text{-alkyl})$ , or a cation of a pharmaceutically acceptable base;

20  $R_{12}$  is F,  $X_6$  is CH,  $X_7$  is  $CH_2$  and  $R_8$  is H, alkyl of 1 to 6 carbons, -  
21  $CH_2O(C_{1-6}\text{-alkyl})$ , or a cation of a pharmaceutically acceptable base, and

22  $R_{12}$  is H,  $X_6$  is N,  $X_7$  is  $CH_2$  and  $R_8$  is H, alkyl of 1 to 6 carbons, -  
23  $CH_2O(C_{1-6}\text{-alkyl})$ , or a cation of a pharmaceutically acceptable base.

24 64. A method in accordance with Claim 63 wherein the compound is

25 selected from the group of compounds wherein the variables for each

26 compound are defined as follows:

27  $R_{12}$  is H,  $X_6$  is CH,  $X_7$  is  $(CH_3)_2C$  and  $R_8$  is H or a cation of a

28 pharmaceutically acceptable base;

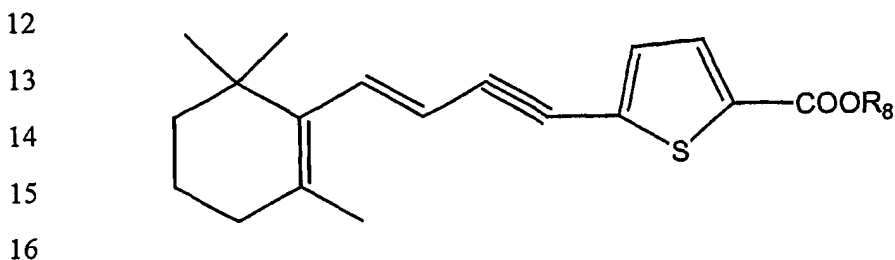
1  $R_{12}$  is H,  $X_6$  is CH,  $X_7$  is  $CH_2$  and  $R_8$  is H or a cation of a  
2 pharmaceutically acceptable base;

3  $R_{12}$  is H,  $X_6$  is CH,  $X_7$  is S and  $R_8$  is H or a cation of a  
4 pharmaceutically acceptable base;

5  $R_{12}$  is F,  $X_6$  is CH,  $X_7$  is  $CH_2$  and  $R_8$  is H or a cation of a  
6 pharmaceutically acceptable base, and

7  $R_{12}$  is H,  $X_6$  is N,  $X_7$  is  $CH_2$  and  $R_8$  is H or a cation of a  
8 pharmaceutically acceptable base.

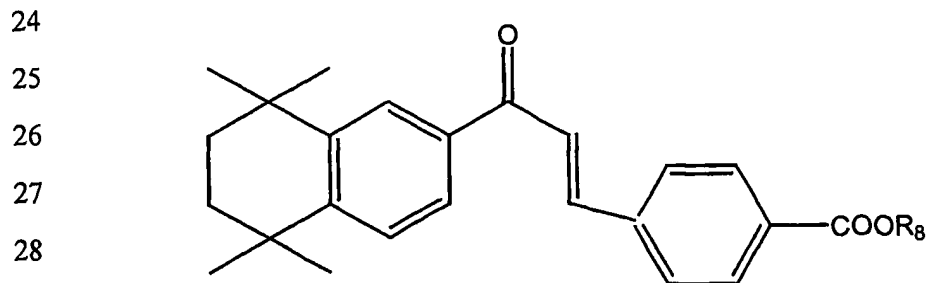
9 65. A method of inhibiting the enzyme cytochrome P450RAI in a  
10 mammal by administering to said mammal an effective dose of a  
11 pharmaceutical composition comprising a compound shown by the formula



17 wherein the variable  $R_8$  is H, alkyl of 1 to 6 carbons,  $-CH_2O(C_{1-6}-$   
18 alkyl), or a cation of a pharmaceutically acceptable base.

19 66. A method in accordance with Claim 65 wherein in the formula of  
20 the compound  $R_8$  is H or a cation of a pharmaceutically acceptable base.

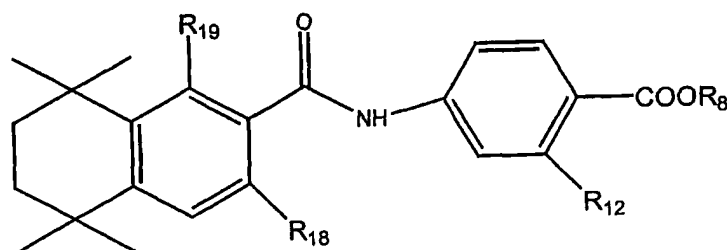
21 67. A method of inhibiting the enzyme cytochrome P450RAI in a  
22 mammal by administering to said mammal an effective dose of a  
23 pharmaceutical composition comprising a compound shown by the formula



1 wherein the variable  $R_8$  is H, alkyl of 1 to 6 carbons,  $-\text{CH}_2\text{O}(\text{C}_{1-6}$ -  
2 alkyl), or a cation of a pharmaceutically acceptable base.

3 68. A method in accordance with Claim 67 wherein in the formula of  
4 the compound  $R_8$  is H or a cation of a pharmaceutically acceptable base.

5 69. A method of inhibiting the enzyme cytochrome P450RAI in a  
6 mammal by administering to said mammal an effective dose of a  
7 pharmaceutical composition comprising a compound selected from the group  
8 of compounds wherein the variables for each compound are defined as  
9 follows with reference to the formula below:



16  $R_{12}$  is F,  $R_{18}$  is H,  $R_{19}$  is H and  $R_8$  is H, alkyl of 1 to 6 carbons, -  
17  $\text{CH}_2\text{O}(\text{C}_{1-6}$ -alkyl), or a cation of a pharmaceutically acceptable base, and

18  $R_{12}$  is H,  $R_{18}$  is OH,  $R_{19}$  is F and  $R_8$  is H, alkyl of 1 to 6 carbons, -  
19  $\text{CH}_2\text{O}(\text{C}_{1-6}$ -alkyl), or a cation of a pharmaceutically acceptable base.

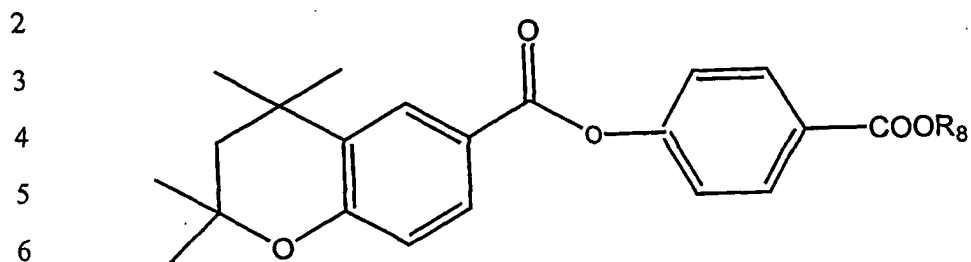
20 70. A method in accordance with Claim 69 wherein the compound is  
21 selected from the group of compounds wherein the variables for each  
22 compound are defined as follows:

23  $R_{12}$  is F,  $R_{18}$  is H,  $R_{19}$  is H and  $R_8$  is H or a cation of a  
24 pharmaceutically acceptable base, and

25  $R_{12}$  is H,  $R_{18}$  is OH,  $R_{19}$  is F and  $R_8$  is H or a cation of a  
26 pharmaceutically acceptable base.

27 71. A method of inhibiting the enzyme cytochrome P450RAI in a  
28 mammal by administering to said mammal an effective dose of a

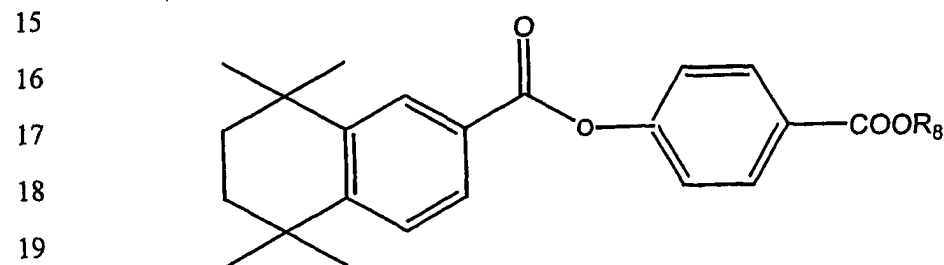
1 pharmaceutical composition comprising a compound shown by the formula



7  
8 wherein the variable  $R_8$  is H, alkyl of 1 to 6 carbons,  $-\text{CH}_2\text{O}(\text{C}_{1-6}$   
9 alkyl), or a cation of a pharmaceutically acceptable base.

10 72. A method in accordance with Claim 71 wherein in the formula of  
11 the compound  $R_8$  is H or a cation of a pharmaceutically acceptable base.

12 73. A method of inhibiting the enzyme cytochrome P450RAI in a  
13 mammal by administering to said mammal an effective dose of a  
14 pharmaceutical composition comprising a compound shown by the formula

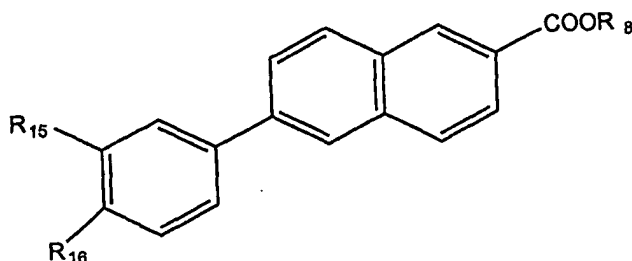


20  
21 wherein the variable  $R_8$  is H, alkyl of 1 to 6 carbons,  $-\text{CH}_2\text{O}(\text{C}_{1-6}$   
22 alkyl), or a cation of a pharmaceutically acceptable base.

23 74. A method in accordance with Claim 73 wherein in the formula of  
24 the compound  $R_8$  is H or a cation of a pharmaceutically acceptable base.

25 75. A method of inhibiting the enzyme cytochrome P450RAI in a  
26 mammal by administering to said mammal an effective dose of a  
27 pharmaceutical composition comprising a compound selected from the group  
28 of compounds wherein the variables for each compound are defined as

1 follows with reference to the formula below:



8  $R_{15}$  is 1-adamantyl,  $R_{16}$  is OH and  $R_8$  is H, alkyl of 1 to 6 carbons, -  
9  $CH_2O(C_{1-6}\text{-alkyl})$ , or a cation of a pharmaceutically acceptable base, and

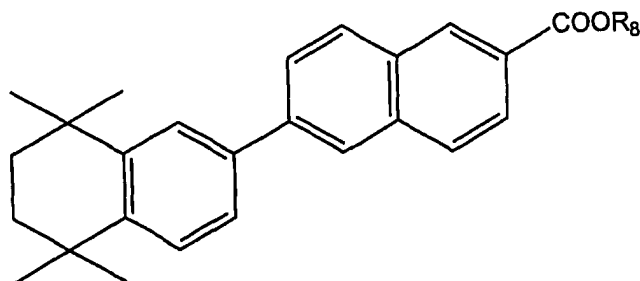
10  $R_{15}$  is 1-adamantyl,  $R_{16}$  is  $OCH_3$  and  $R_8$  is H, alkyl of 1 to 6 carbons, -  
11  $CH_2O(C_{1-6}\text{-alkyl})$ , or a cation of a pharmaceutically acceptable base.

12 76. A method in accordance with Claim 75 wherein the compound is  
13 selected from the group of compounds wherein the variables for each  
14 compound are defined as follows:

15  $R_{15}$  is 1-adamantyl,  $R_{16}$  is OH and  $R_8$  is H or a cation of a  
16 pharmaceutically acceptable base, and

17  $R_{15}$  is 1-adamantyl,  $R_{16}$  is  $OCH_3$  and  $R_8$  is H or a cation of a  
18 pharmaceutically acceptable base.

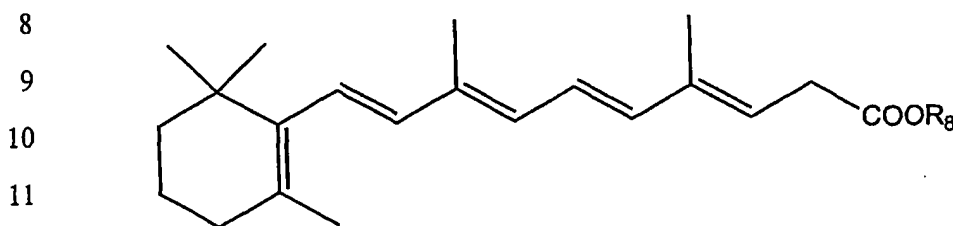
19 77. A method of inhibiting the enzyme cytochrome P450RAI in a  
20 mammal by administering to said mammal an effective dose of a  
21 pharmaceutical composition comprising a compound shown by the formula



1 wherein the variable  $R_8$  is H, alkyl of 1 to 6 carbons,  $-\text{CH}_2\text{O}(\text{C}_{1-6}$   
 2 alkyl), or a cation of a pharmaceutically acceptable base.

3 78. A method in accordance with Claim 77 wherein in the formula of  
 4 the compound  $R_8$  is H or a cation of a pharmaceutically acceptable base.

5 79. A method of inhibiting the enzyme cytochrome P450RAI in a  
 6 mammal by administering to said mammal an effective dose of a  
 7 pharmaceutical composition comprising a compound shown by the formula



13 wherein the variable  $R_8$  is H, alkyl of 1 to 6 carbons,  $-\text{CH}_2\text{O}(\text{C}_{1-6}$   
 14 alkyl), or a cation of a pharmaceutically acceptable base.

15 80. A method in accordance with Claim 79 wherein in the formula of  
 16 the compound  $R_8$  is H or a cation of a pharmaceutically acceptable base.

17 81. A method of providing a compound which is an inhibitor of the  
 18 enzyme cytochrome P450RAI, the method comprising:

19 identifying a compound that has activity as a retinoid in an art  
 20 recognized assay which demonstrates retinoid-like activity, the retinoid  
 21 compound having a formula such that it includes a benzoic acid, benzoic acid  
 22 ester, naphthoic acid, naphthoic acid ester or heteroaryl carboxylic acid or  
 23 ester moiety, with a partial structure of  $-\text{A}(\text{R}_2)-(\text{CH}_2)_n-\text{COOR}_8$  where  $n$  is  
 24 0,  $\text{A}$  is a phenyl or naphthyl group, or heteroaryl selected from a group  
 25 consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl,  
 26 thiazolyl, oxazolyl, imidazolyl and pyrrazolyl, said phenyl, naphthyl and  
 27 heteroaryl groups being optionally substituted with one or two  $\text{R}_2$  groups;  $\text{R}_2$   
 28 is independently H, alkyl of 1 to 6 carbons, F, Cl, Br, I,  $\text{CF}_3$ , fluoro substituted



1 alkyl of 1 to 6 carbons, alkoxy of 1 to 6 carbons, or alkylthio of 1 to 6 carbons  
2 and  $R_8$  is H, alkyl of 1 to 6 carbons,  $-\text{CH}_2\text{O}(\text{C}_{1-6}\text{-alkyl})$ , or a cation of a  
3 pharmaceutically acceptable base, and

4 selecting a compound that is a homolog of the previously identified  
5 retinoid compound where in the formula of the homolog  $n$  is 1 or 2.

6 **82.** A method in accordance with Claim 81 wherein a homolog is  
7 selected where in the formula of the homolog  $n$  is 1.

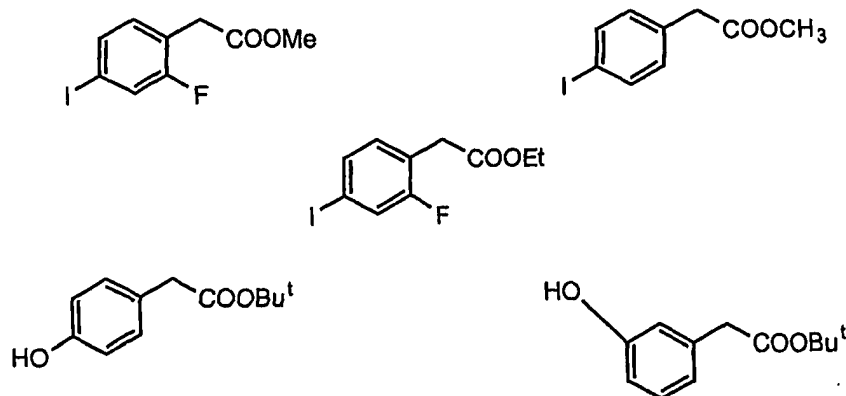
8 **83.** A method in accordance with Claim 81 further comprising the step  
9 of synthesizing the selected homolog.

10 **84.** A method in accordance with Claim 83 wherein a homolog is  
11 synthesized where in the formula of the homolog  $n$  is 1.

12 **85.** A method in accordance with Claim 83 wherein the step of  
13 synthesizing the homolog utilizes a homologation procedure wherein a chain  
14 of a carboxylic acid or of carboxylic ester of the partial formula  $-\text{A}(\text{R}_2)-$   
15  $(\text{CH}_2)_n-\text{COOR}_8$  is lengthened by adding one or two  $(\text{CH}_2)$  units.

16 **86.** A method in accordance with Claim 85 wherein the step of  
17 synthesizing the homolog utilizes *Arndt-Eistert* method of synthesis.

18 **87.** A method in accordance with Claim 84 where the step of  
19 synthesizing the homolog includes a reaction with a reagent selected from the  
20 formulas



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